Mitochondria in Space: The Data in Nutshell

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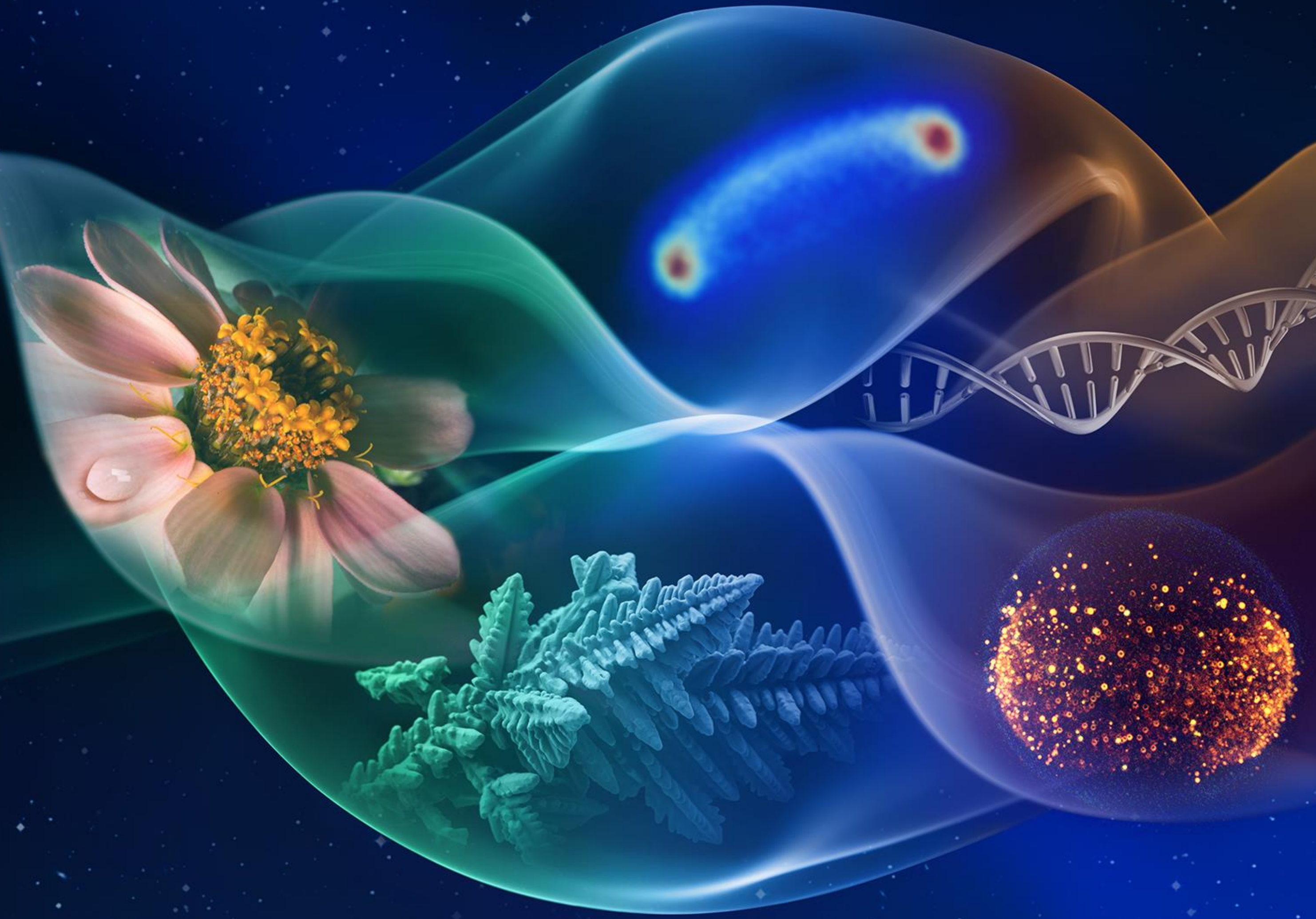
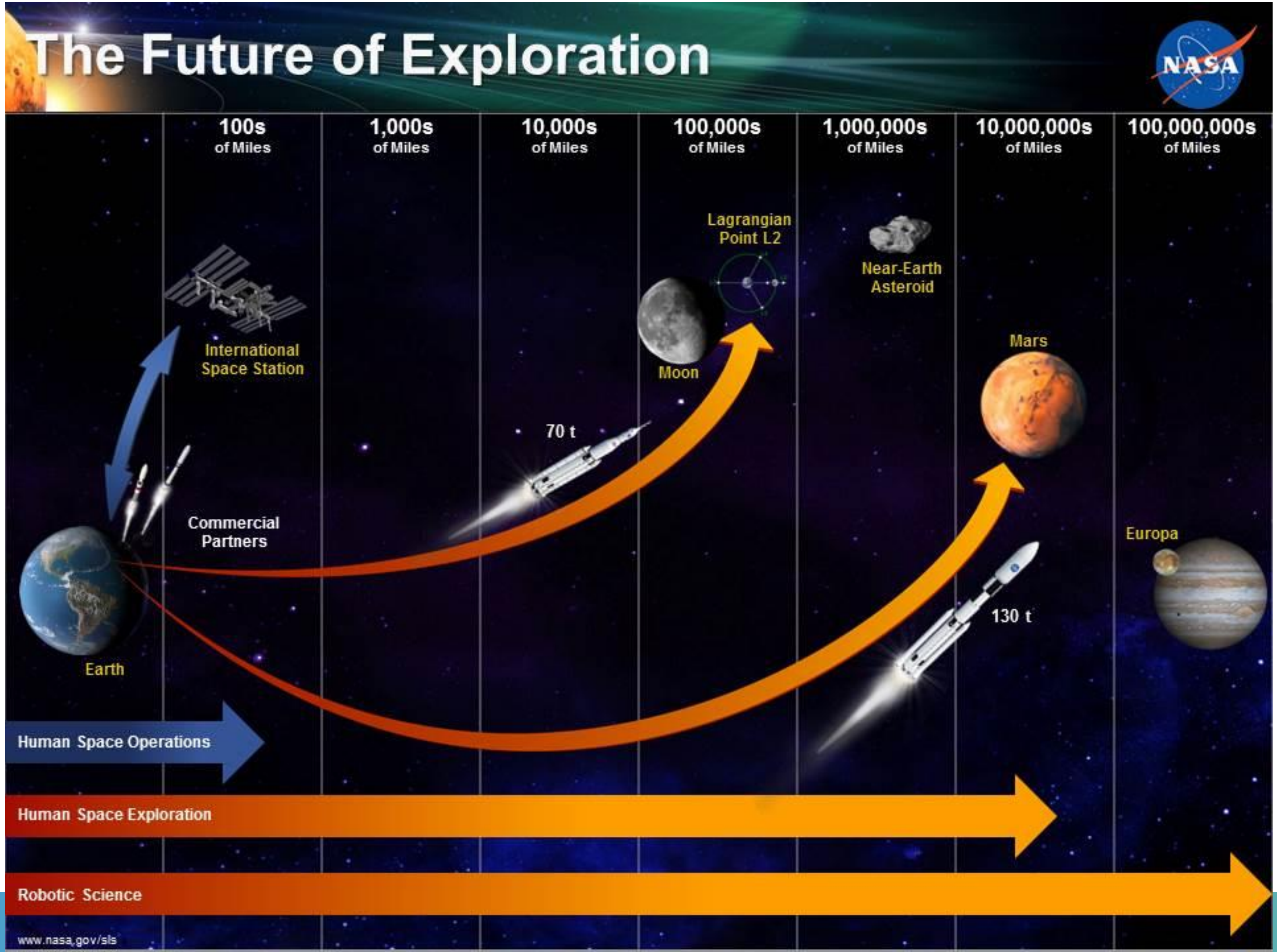
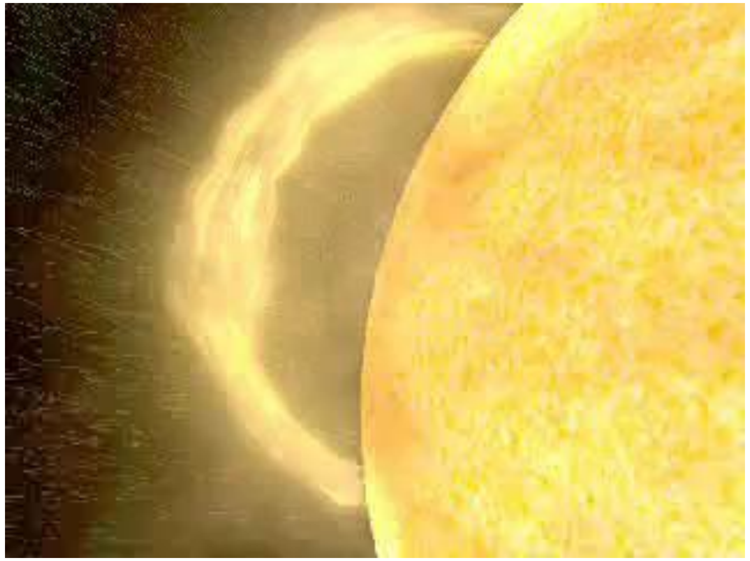
Background on Spaceflight, Experiments, and Resources for the Data That was used for the Mitochondrial project

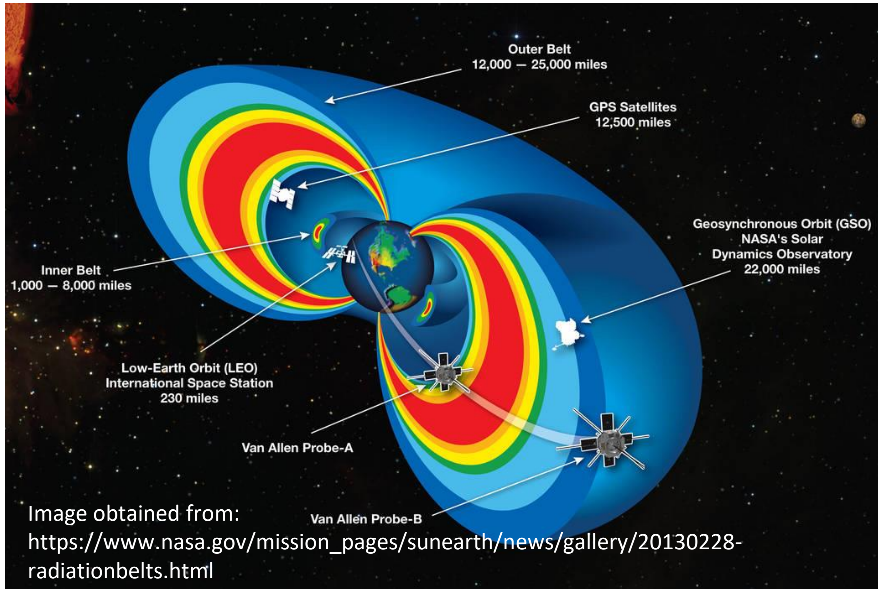


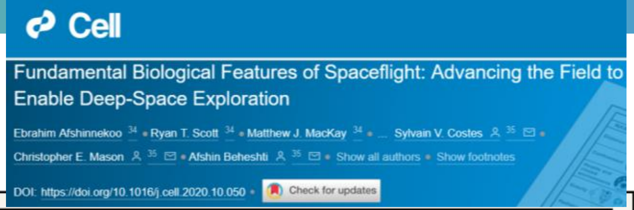
Why Care About Space Biology Research



Space Environment



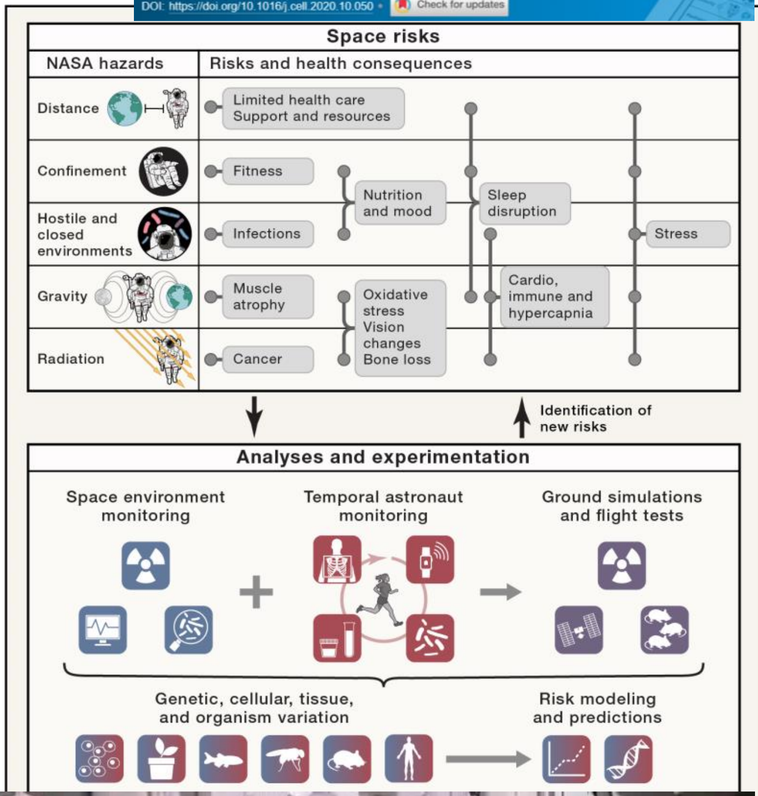



Cell

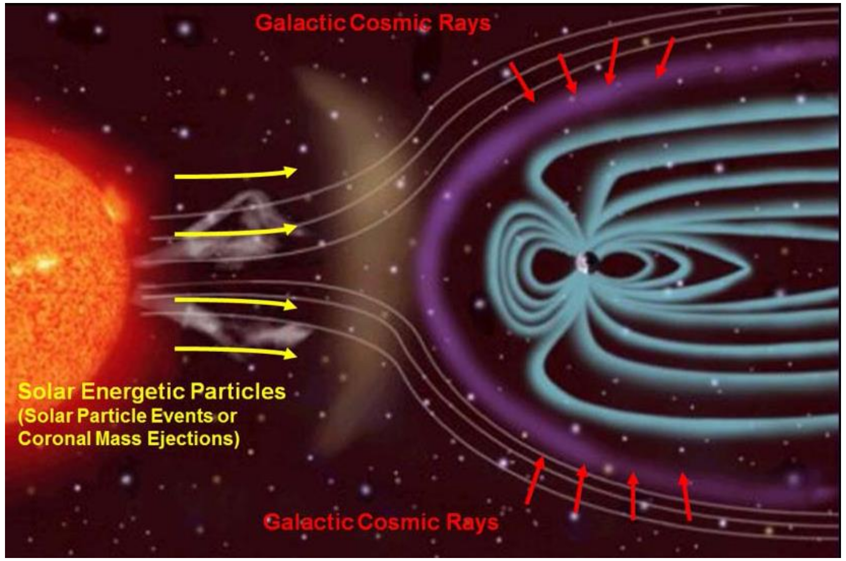
Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration

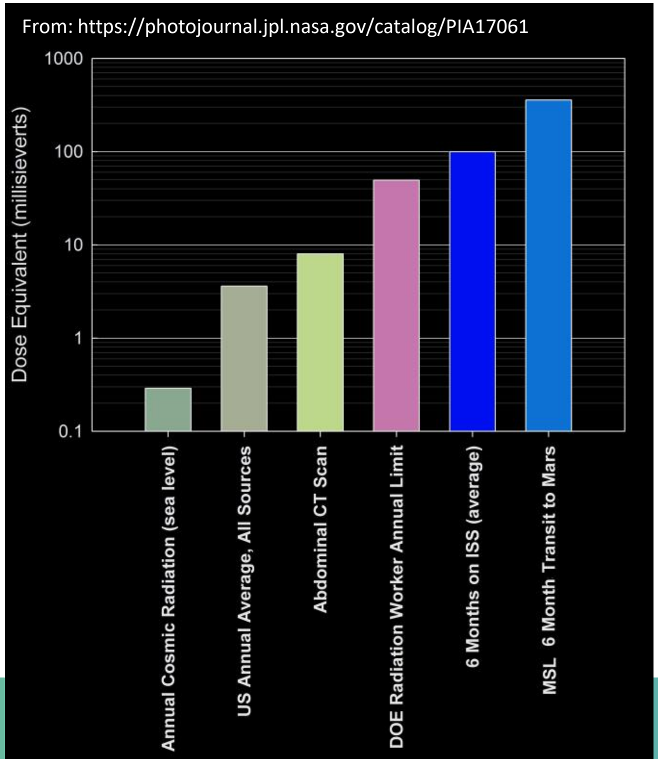
Ebrahim Afshinnekoo • Ryan T. Scott • Matthew J. MacKay • ... Sylvain V. Costes • Christopher E. Mason • Afshin Beheshti • Show all authors • Show footnotes

DOI: https://doi.org/10.1016/j.cell.2020.10.050 • Check for updates



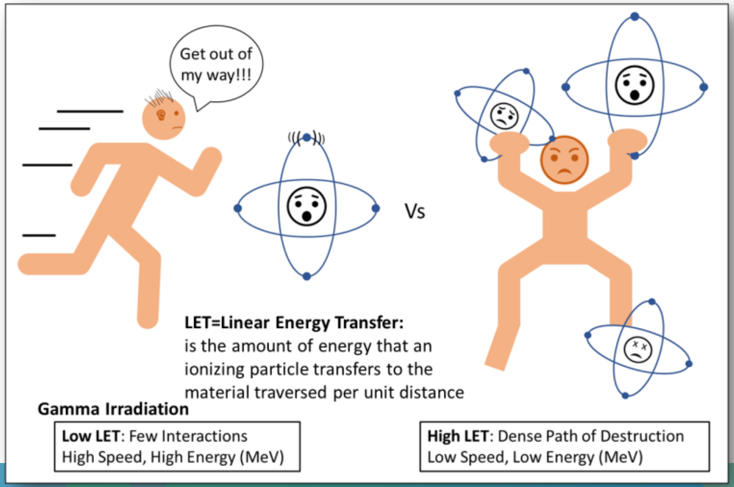
Radiation

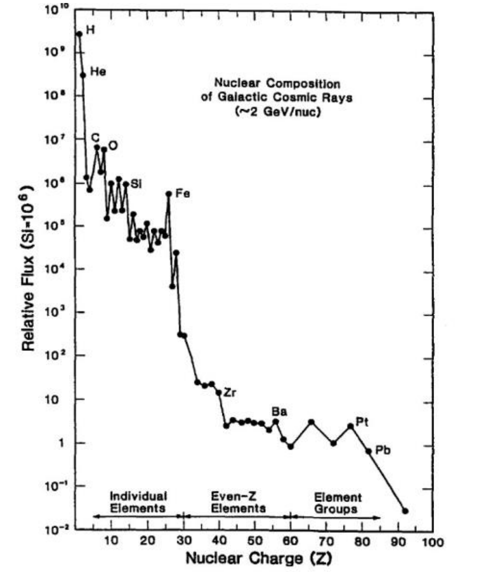




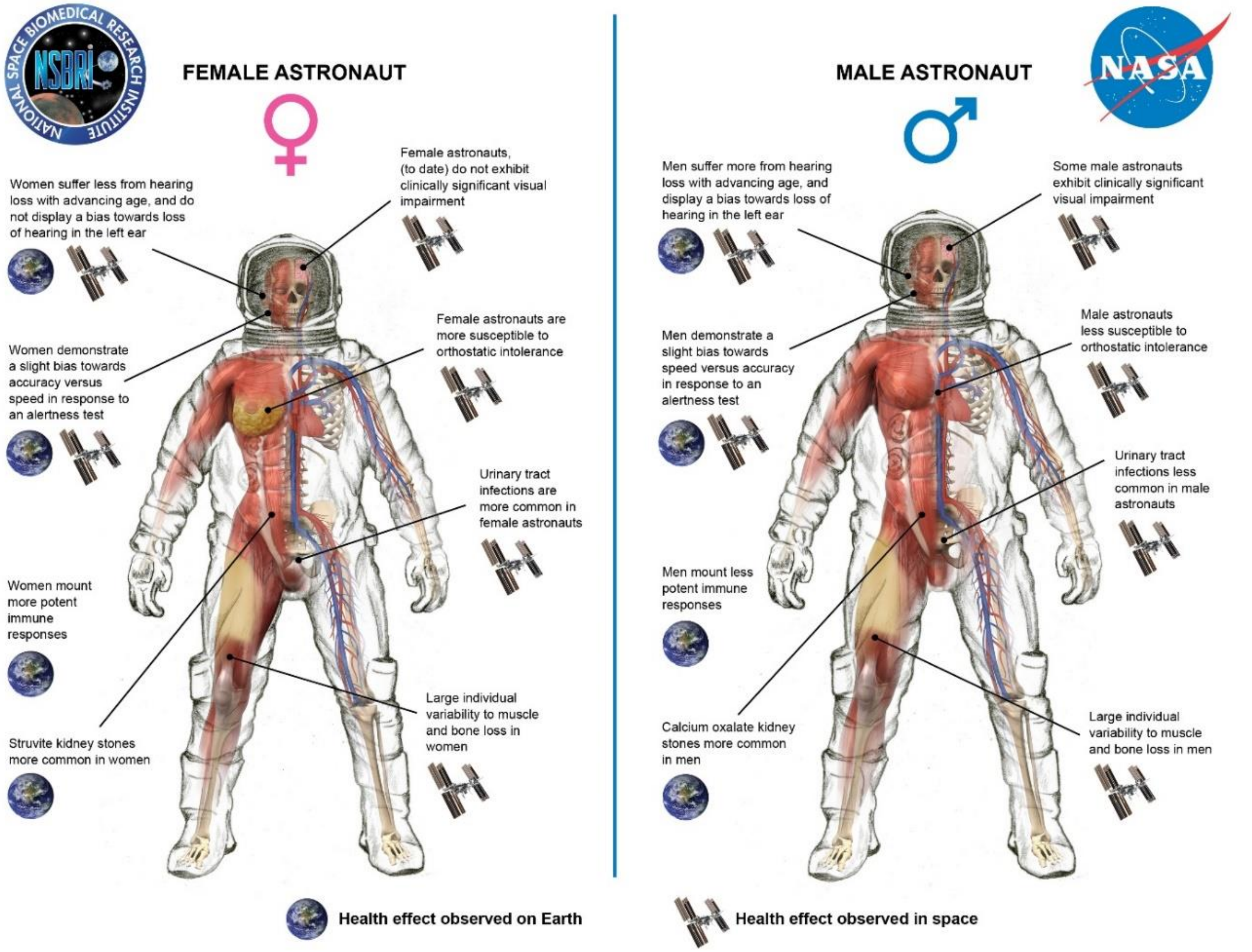
Microgravity

Galactic Cosmic Radiation (High LET) – a cautionary tale





Space Environment Health Risks On Astronauts



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Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration

Ebrahim Afshinnekoo • Ryan T. Scott • Matthew J. MacKay • … Sylvain V. Costes • Christopher E. Mason • Afshin Beheshti • Show all authors • Show footnotes

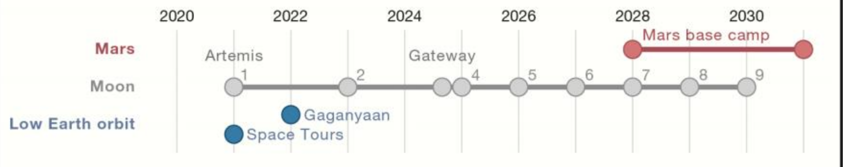
DOI: https://doi.org/10.1016/j.cell.2020.10.050 • Check for updates

A Mission and long-term health risks

Mission type	Low Earth orbit		Low Earth orbit		Deep space sortie		Lunar visit/habitat		Deep space journey		Planetary visit/habitat	
Mission duration	6 months		12 months		1 month		12 months		12 months		36 months	
Return duration	<= 1 day		<= 1 day		< 5 days		5 days		Weeks/months		Months	
Radiation	Van Allen		Van Allen		Deep Space		Lunar		Deep Space		Variable	
Gravity	Micro		Micro		Micro		1/6g		Micro		Variable	
Health risks	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term	Mission	Long-term
Renal	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	High	High	High	High
Medical	Medium	Medium	Medium	Medium	Medium	Low	Medium	Medium	High	High	High	High
SANS	Medium	Medium	Medium	Medium	Low	Low	Medium	Medium	High	High	High	High
Arrhythmia	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	High	Medium	High	Medium
BMed	Medium	Medium	Medium	Medium	Medium	Low	Medium	Medium	Medium	Medium	High	High
Occupant protection	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium
Hypobaric hypoxia	Medium	Medium	Medium	Medium	Medium	Low	Medium	Medium	Medium	Medium	Medium	Medium
EVA	Low	Medium	Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	High
Degen	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	High	Low	High
CNS	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium	Medium	Medium	Medium
Team	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	High	Medium
Sleep	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium	Medium	Medium
Sensorimotor	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium
Cancer	Low	Medium	Low	Medium	Low	Low	Low	Medium	Low	High	Low	High
Muscle	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium
Aerobic	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium
Immune	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium
Microhost	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Medium
DCS	Low	Low	Low	Low	Medium	Low	Medium	Low	Medium	Low	Medium	Low
Stability	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	High
OI	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium	Low
ARS	Low		Low		Low		Low		Low		Low	
Dust							Medium	Medium				

Risk level ● Low ● Medium ● High

B Planned human missions

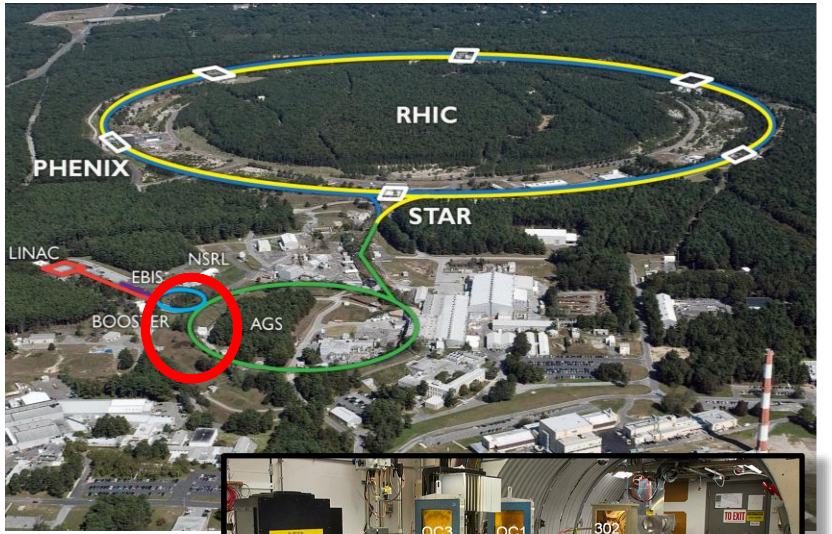


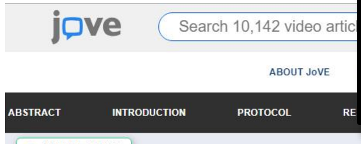
Type of Experiments Related to Space Biology

Experiments Done in Space

Space Radiation Simulated Experiments

Brookhaven National Laboratory



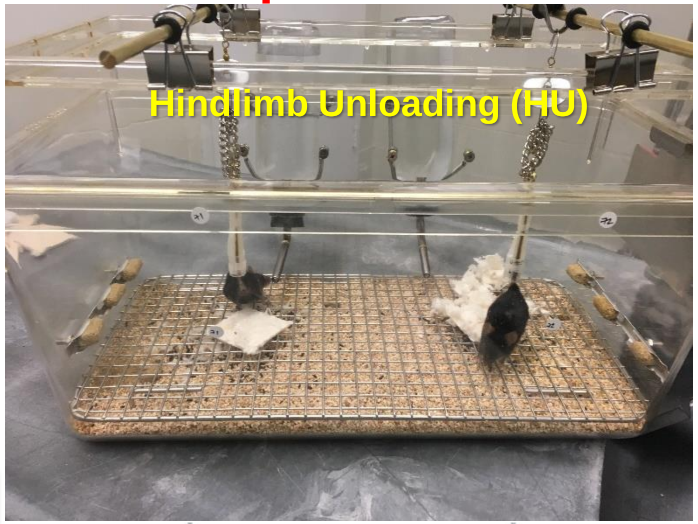


Exploring the Effects of Spaceflight on Mouse Physiology using the Open Access NASA GeneLab Platform

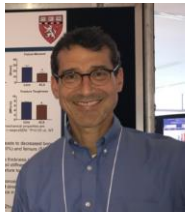
Afshin Beheshti[1], Yasaman Shirazi-Fard[2], Sungshin Choi[1], Daniel Berrios[3], Samrawit G. Gebre[1], Jonathan M. Galazka[2], Sylvain V. Costes[2]

[1]WYLE Labs, Space Biosciences Division, NASA Ames Research Center, [2]Space Biosciences Division, NASA Ames Research Center, [3]USRA, NASA Ames Research Center

Microgravity Simulated Experiments



Partial Weight Bearing Rat Model



Seward Rutkove

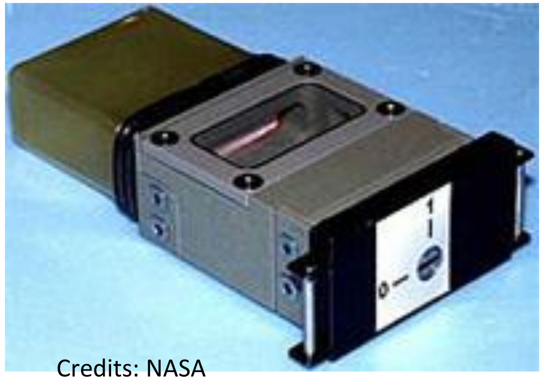
Marie Mortreux

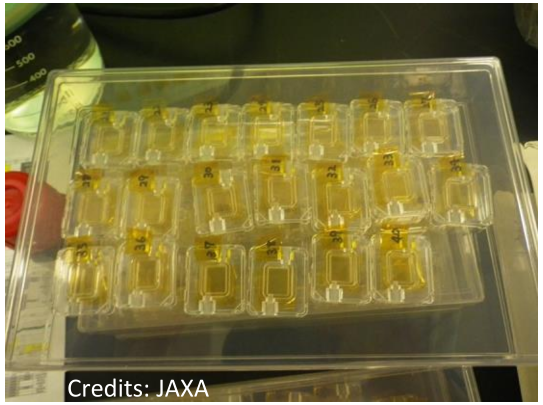
Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

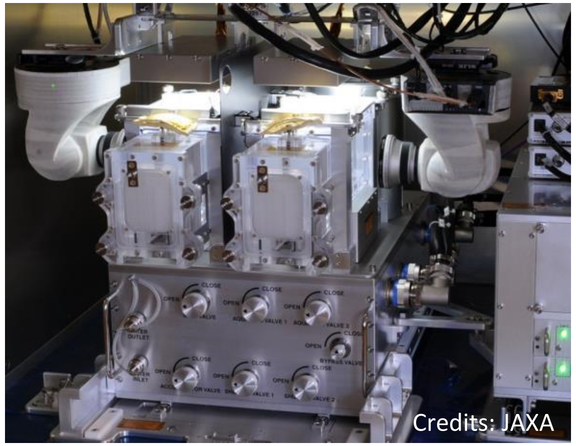
https://www.rutkovelab.org/nasa/

Other Types of Experiments on the ISS


Credits: NASA


Credits: JAXA

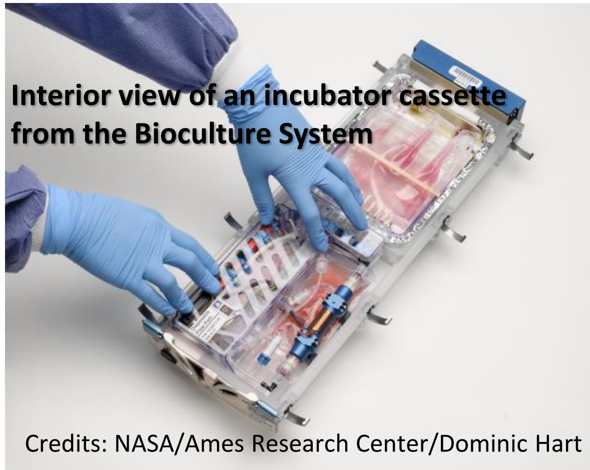
C. elegans culture chambers for the Space Aging experiment aboard the ISS


Credits: JAXA

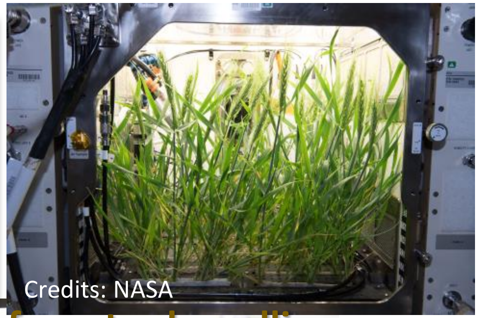

Credits: NASA

The Zebrafish Muscle investigation employs the ISS Aquatic Habitat, an aquarium in microgravity.

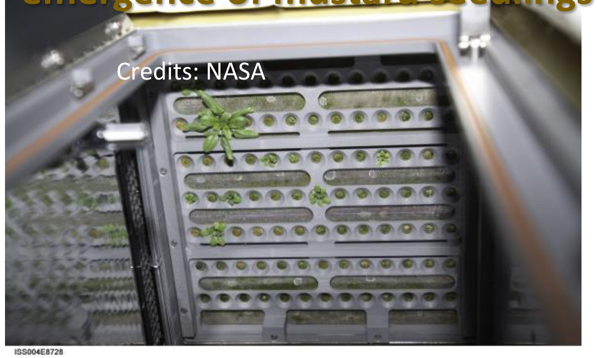

Credits: NASA

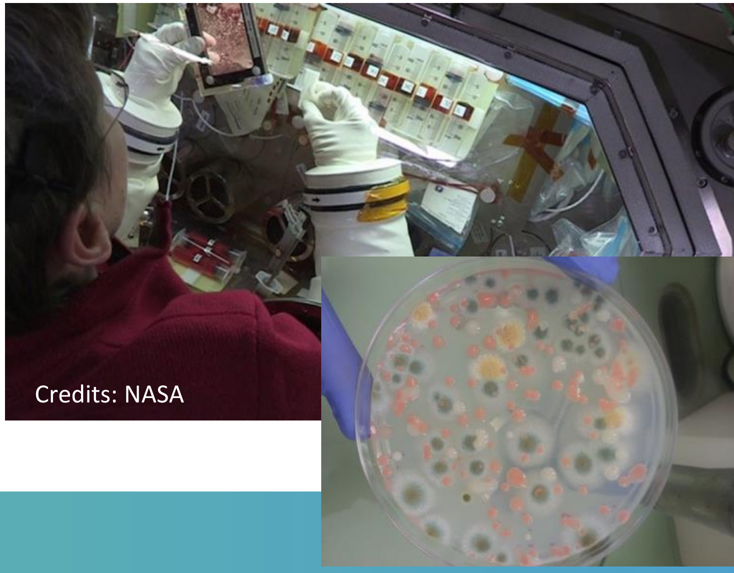

Interior view of an incubator cassette from the Bioculture System

Credits: NASA/Ames Research Center/Dominic Hart


Credits: NASA

emergence of mustard seedlings


Credits: NASA


Credits: NASA

Lots of Papers Published on Space Biology in 11/2020!!

https://www.cell.com/c/the-biology-of-spaceflight

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Related resources ↓ Contributing lab groups ↓ Consortia Hub ↗

The biology of spaceflight

As humankind reaches for the stars to journey to the next frontier in space, research on spaceflight biology is critical for understanding how living systems, including human health, may be affected by spaceflight and space exploration. This special collection on the biology of spaceflight, published in *Cell* and other Cell Press journals, includes research articles, short communications, and a review article that cover studies with model systems and astronaut samples. The work, which was done in collaboration between NASA and other space agencies around the world, uncovers the impact of known hazards of spaceflight, such as radiation and microgravity, and discusses the standards for multi-omics from space and the preparations needed for Mars and other missions in the next two decades.

Cell   Log in

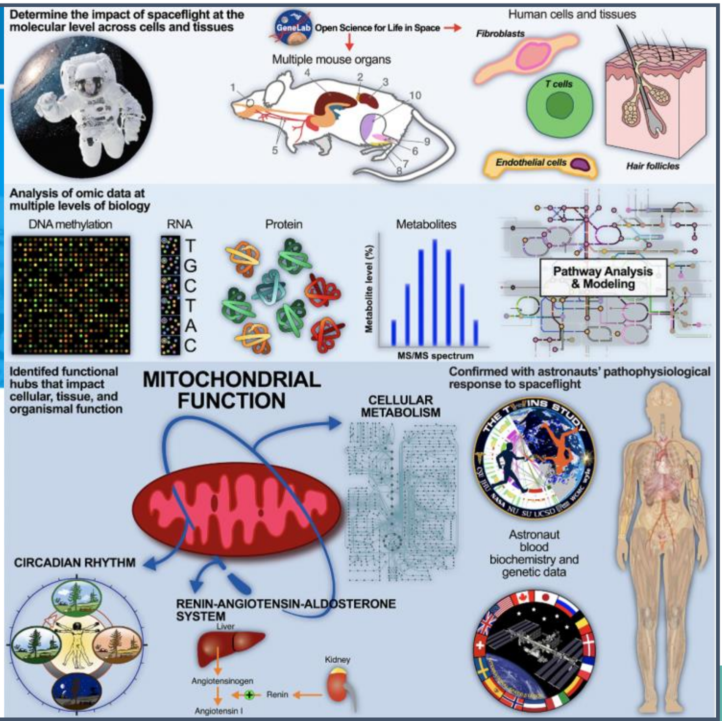
ARTICLE | VOLUME 183, ISSUE 5, P1185-1201.E20, NOVEMBER 25, 2020

Comprehensive Multi-omics Analysis Reveals Mitochondrial Stress as a Central Biological Hub for Spaceflight Impact

Willian A. da Silveira [23] • Hossein Fazelinia [23] • Sara Brin Rosenthal [23] • ...
Christopher E. Mason [24] • Sylvain V. Costes [24] • Afshin Beheshti [24, 25] • Show all authors

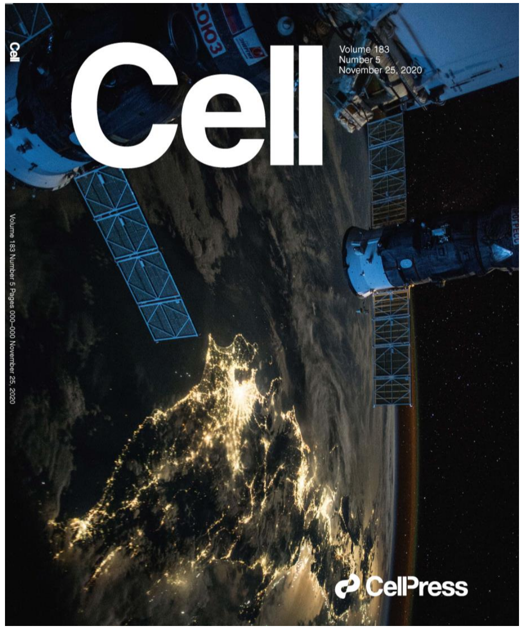
Show footnotes DOI: https://doi.org/10.1016/j.cell.2020.11.002 • Check for updates

PlumX Metrics



Highlights

- Multi-omics analysis and techniques with NASA's GeneLab platform
- The largest cohort of astronaut data to date utilized for analysis
- Mitochondrial dysregulation driving spaceflight health risks
- NASA Twin Study data validates mitochondrial dysfunction during space missions

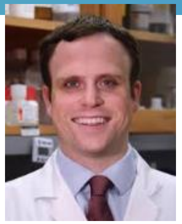


Afshin Beheshti

KBR
We Deliver

Space Biosciences
NASA AMES RESEARCH CENTER

NASA SILICON VALLEY
AMES RESEARCH CENTER



Chris Mason

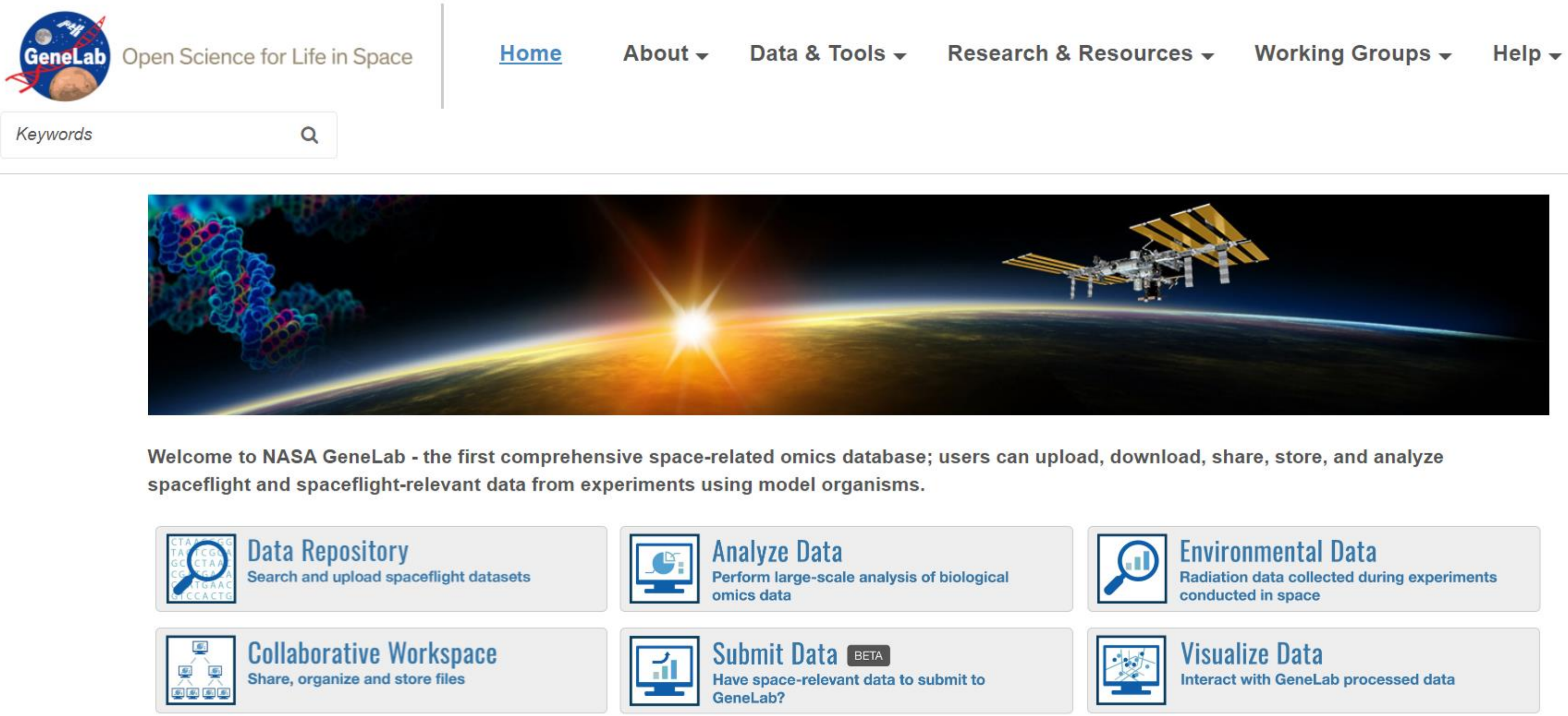
Weill Cornell Medicine

Susan Bailey

COLORADO STATE UNIVERSITY

GeneLab (genelab.nasa.gov)

GeneLab Open Science for Life in Space



Members are now group leads

AWG Members Per Group:

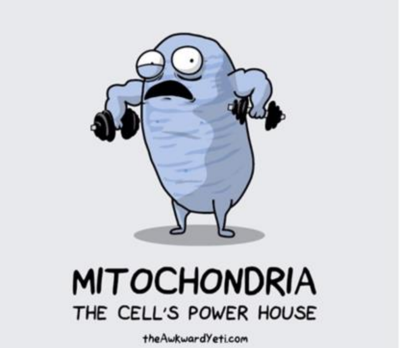
Animal	39
Multi-Omics/System Biology	250+
Plants	44
Microbes	25

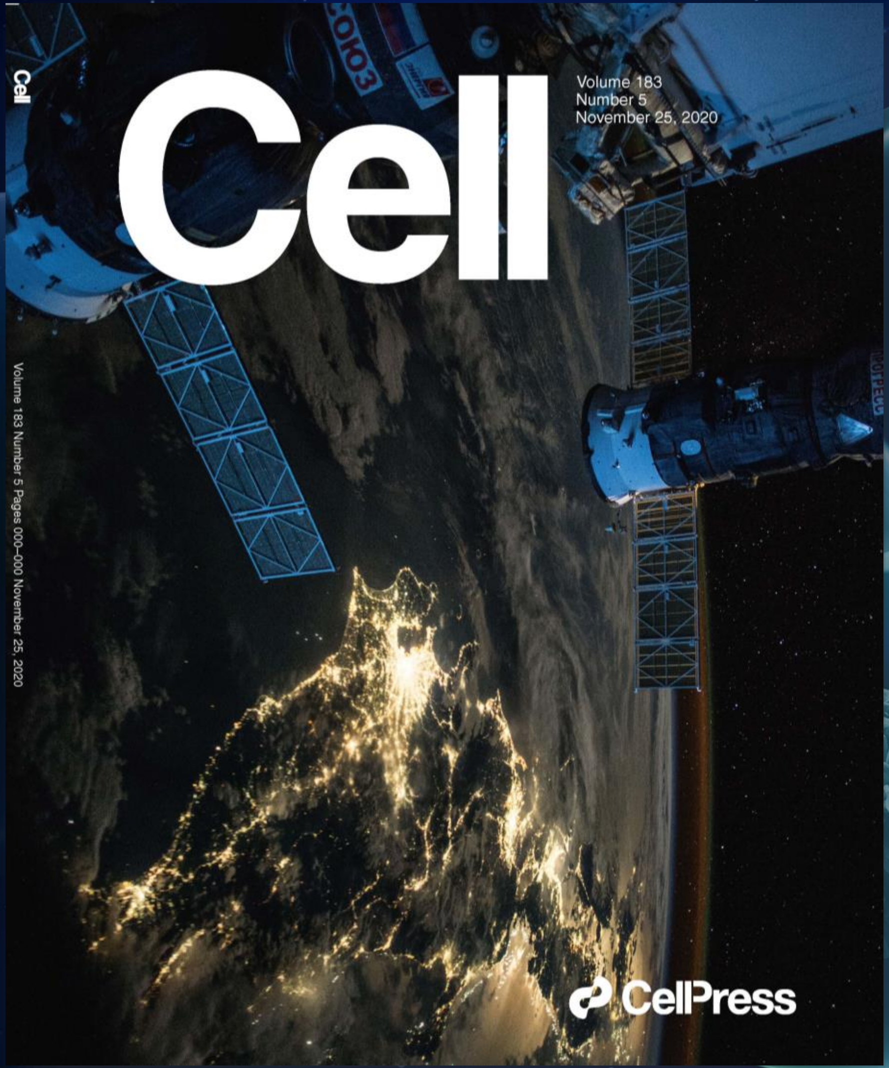
I lead the Multi-Omics Group

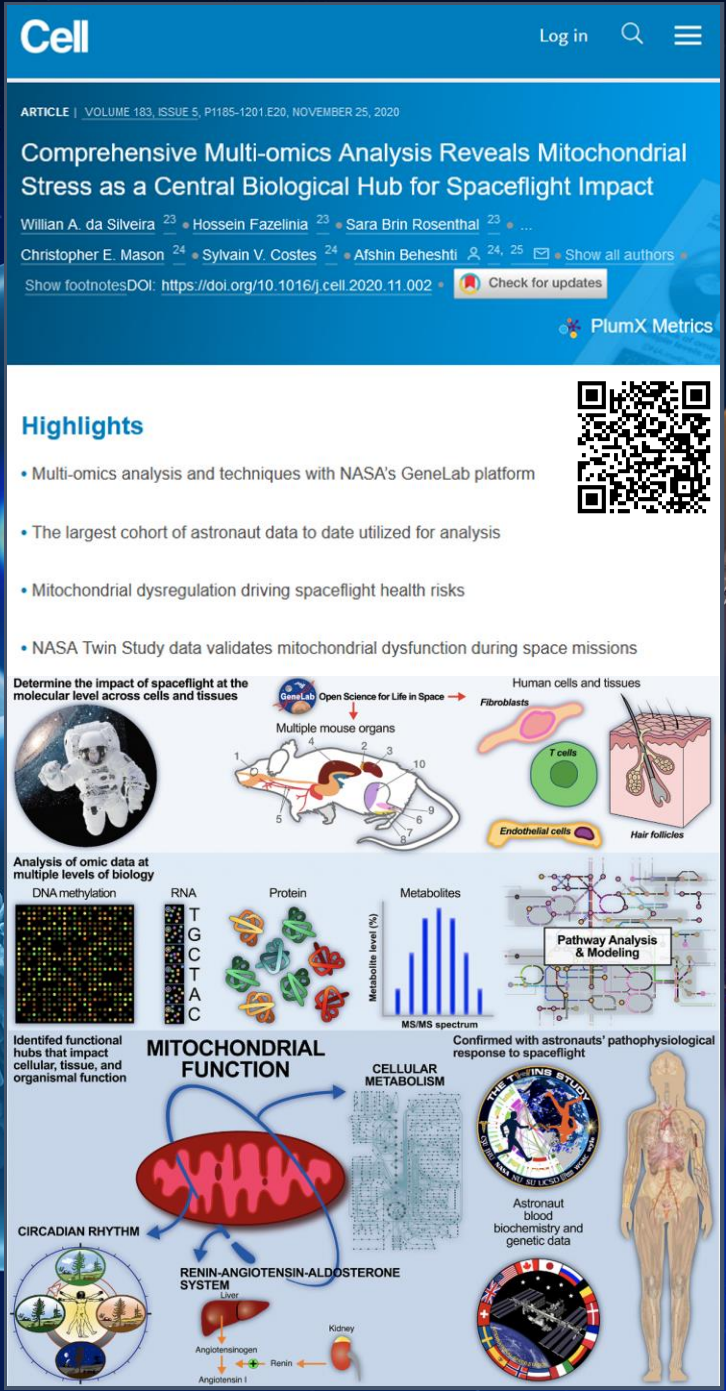
GeneLab Analysis Working Groups (AWGs) *consist of 300+ scientists from multiple space agencies, international institutions, and industry. Scientists meet monthly with each group to analyze data in the GeneLab repository. Majority of members are non-NASA PI’s – many have applied for NASA funding following AWG interactions.*

https://genelab.nasa.gov/awg/join

Spaceflight Impact on the Mitochondria







Analysis Working Group (AWG) Members and Others Involved

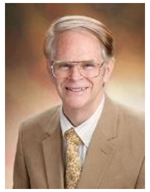

Willian da Silveira

STAFFORDSHIRE UNIVERSITY


Deanne Taylor


Hossein Fazelinia


Komal Rathi


Douglas Wallace


Larry Singh


Benjamin Stear


"Jimmy" Man S Kim

Children's Hospital of Philadelphia

Perelman School of Medicine
University of Pennsylvania

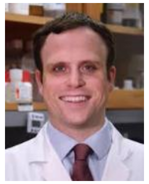

Kathleen Fisch


Brin Rosenthal

UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE


Jonathan Schisler

UNC School of Medicine Pharmacology


Chris Mason


Cem Meydan


Jonathan Foox

Weill Cornell Medicine


Evagelia Laiakis


J. Tyson McDonald

Georgetown University
Georgetown University Medical Center


Jeffrey Willey

WAKE FOREST UNIVERSITY


Yared Kidane

SCOTTISH RITE HOSPITAL FOR CHILDREN

QUEEN'S UNIVERSITY BELFAST


Scott Smith


Brian Crucian


Sara Zwart


Susana Zanello

NASA

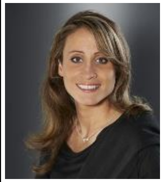
SPACE CENTER HOUSTON
Manned Space Flight Education Foundation

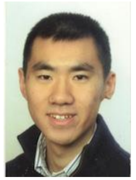

Todd Treangen


Leo Elworth


Nick Sapoval

RICE


Sonja Schrepfer


Dong Wang

UCSF
University of California San Francisco


Stacy Horner


Nandan Gokhale

Duke University School of Medicine


Robert Meller

MOREHOUSE SCHOOL OF MEDICINE


Helio Costa


Kathryn Grabek

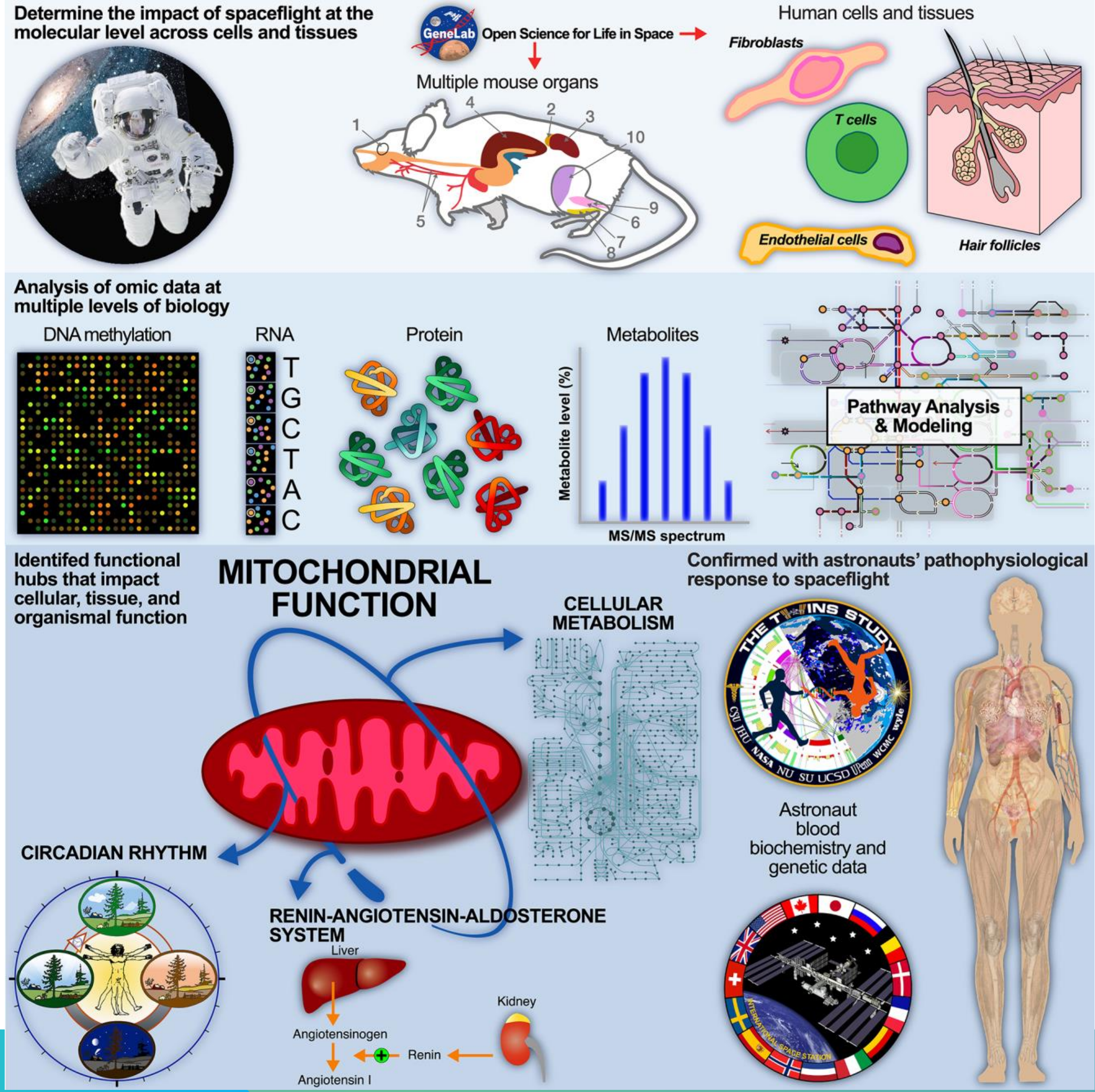
STANFORD UNIVERSITY


Afshin Beheshti


Sylvain Costes

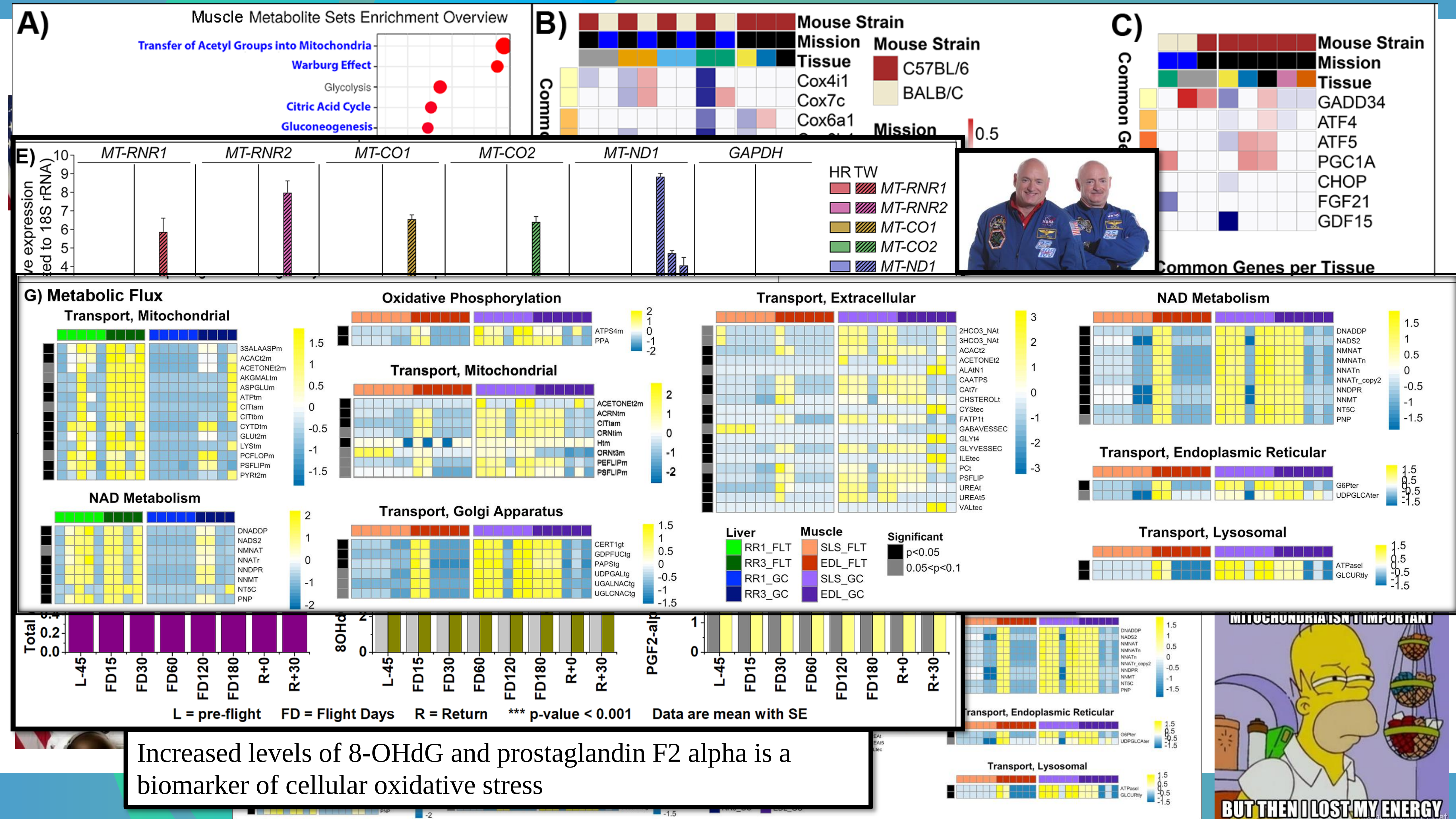
NASA SILICON VALLEY
AMES RESEARCH CENTER

Overview of Data Utilized for this Work and Project



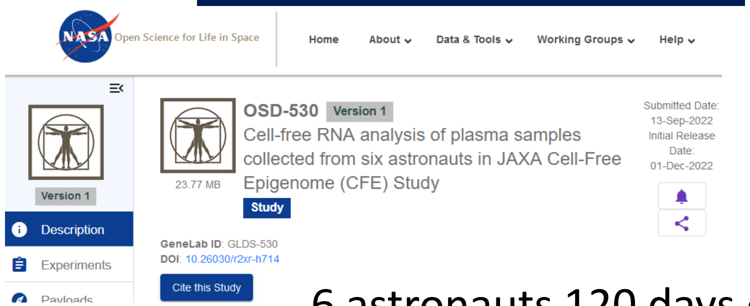
Largest amount of astronaut data in one paper!!

Paper Link:

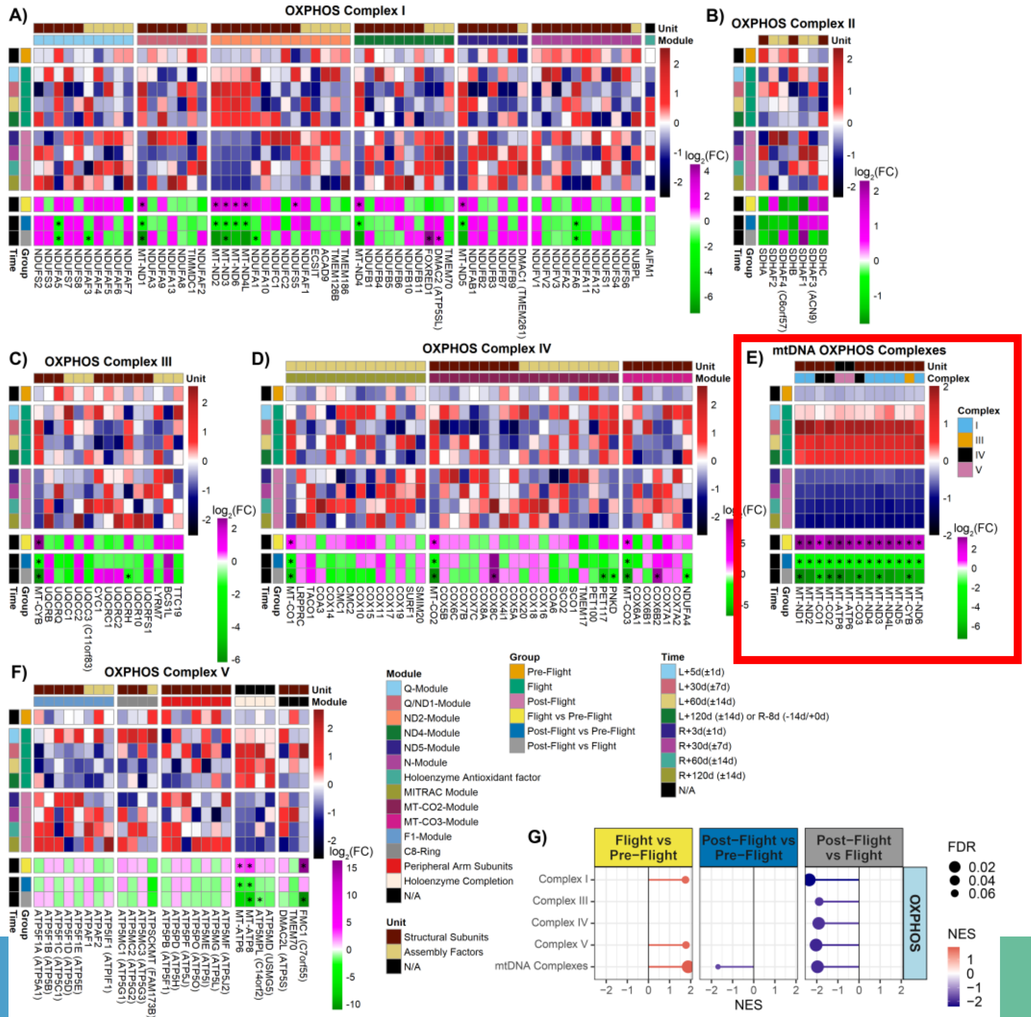


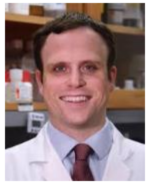
Increased levels of 8-OHdG and prostaglandin F2 alpha is a biomarker of cellular oxidative stress

Ongoing work: Detailed Mitochondrial Analysis on Data from Astronauts



6 astronauts 120 days on the ISS

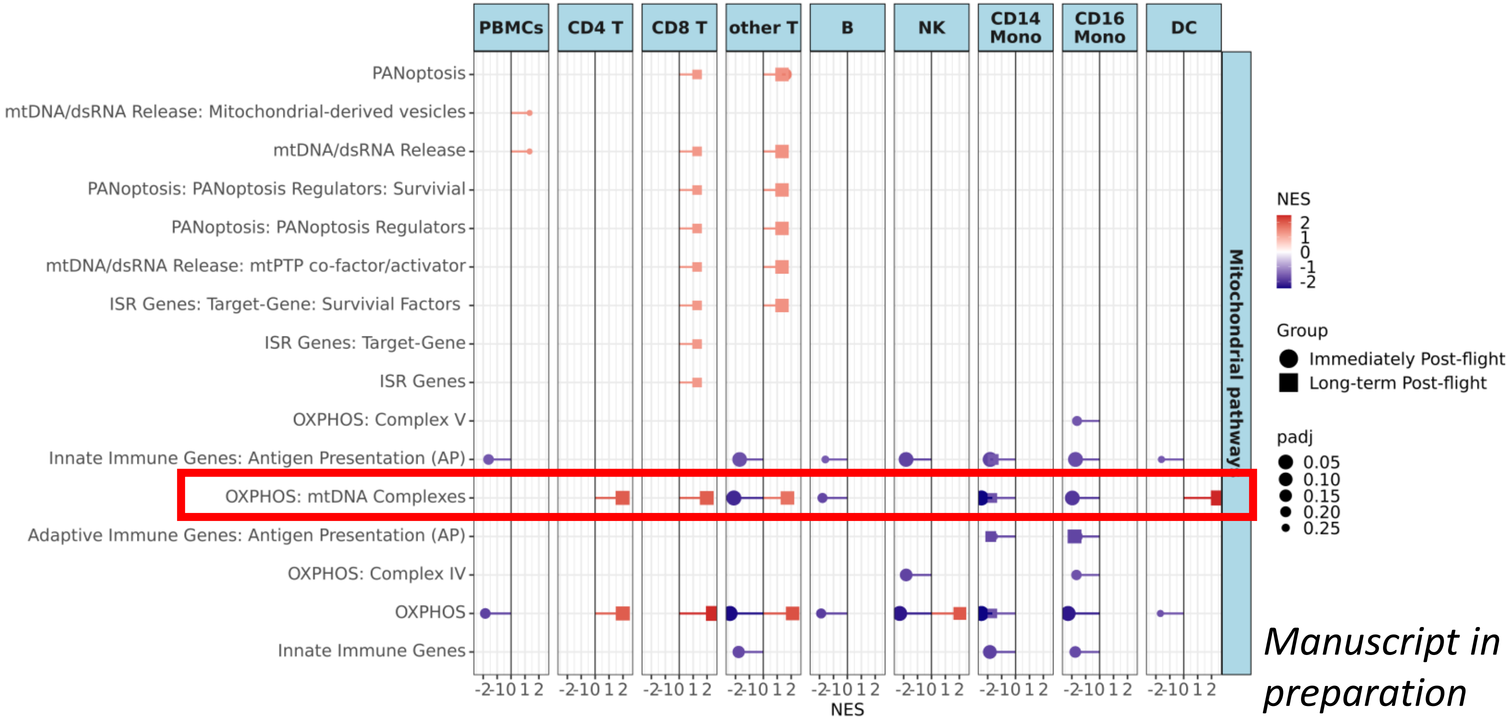





Chris Mason JangKeun Kim

Weill Cornell Medicine

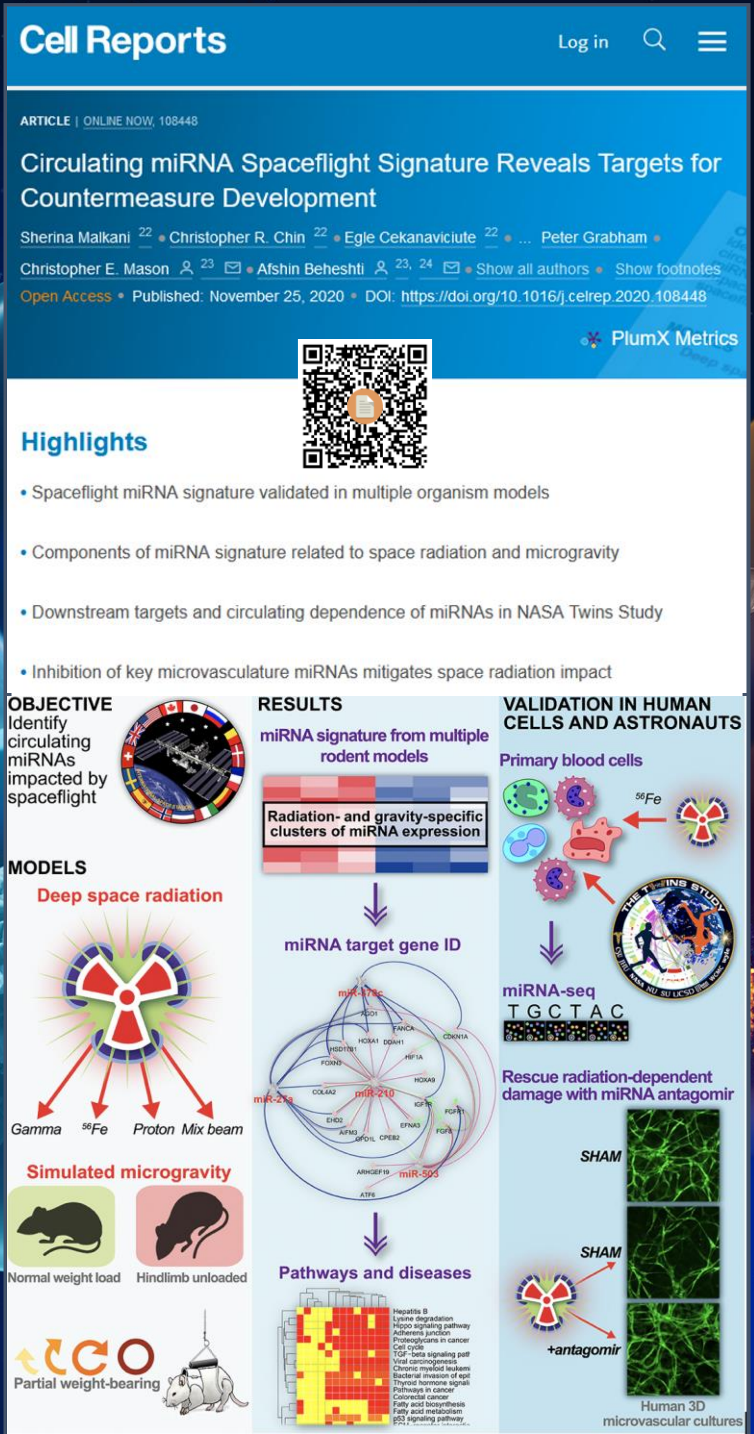
4 astronauts 3 days 590km in elevation (accumulated radiation dose equivalent to ~9 months on ISS



Manuscript in preparation

Can we mitigate the damage caused to the mitochondria in space?

Short answer: Maybe with miRNAs!!



What are miRNAs and why study miRNAs?

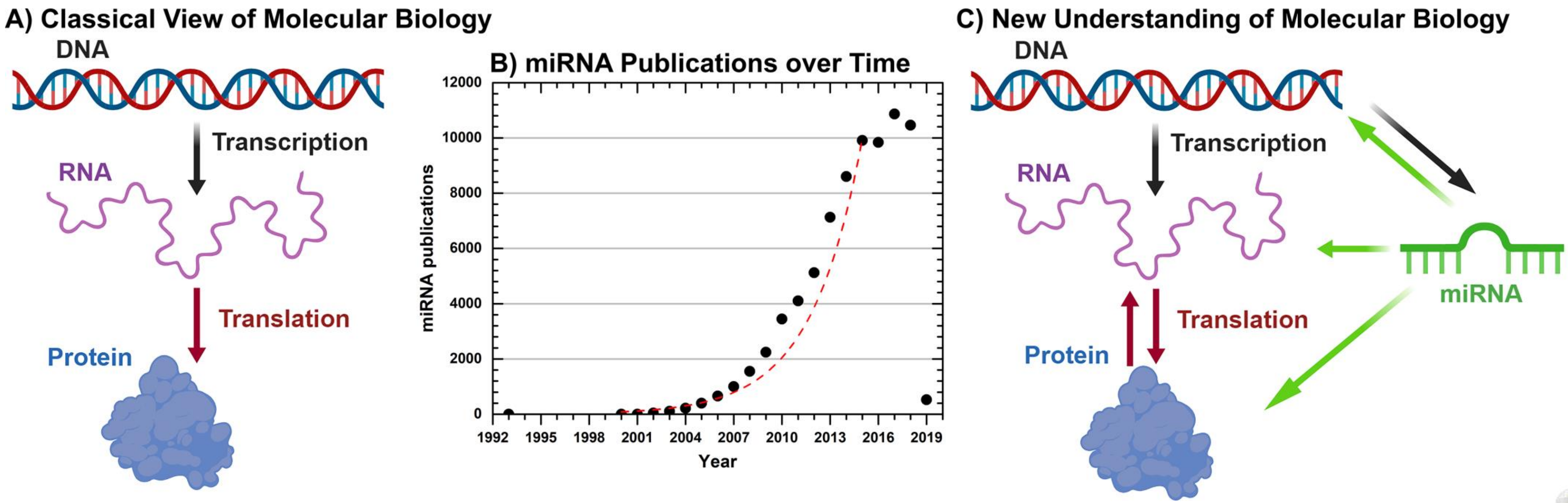
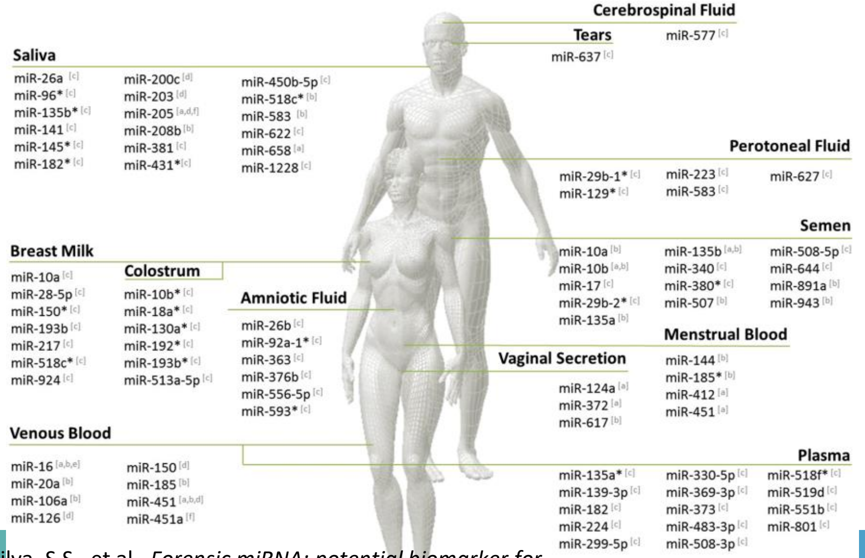


Figure from Vanderburg and Beheshti, MicroRNAs (miRNAs), the Final Frontier: The Hidden Master Regulators Impacting Biological Response in All Organisms Due to Spaceflight, THREE, 2020. (https://three.jsc.nasa.gov/articles/miRNA_Beheshti.cfm)

- **A single miRNA has been estimated to regulate 100s to 1000s of mRNAs.**
- **miRNAs are ~22nt**
- **Due to the size and stability of the miRNAs, it can float freely in the blood.**
- **miRNAs are now known to be involved in all aspects of diseases.**
- **miRNA are not only found in mammals, but everything else living: plants, microbes, fish, C. Elegans, fruit flies, insects, etc…**
- **miRNAs are highly conserved across species.**



Silva, S.S., et al., *Forensic miRNA: potential biomarker for body fluids?* Forensic Sci Int Genet, 2015. **14**: p. 1-10.

Mitochondrial miRNAs (mitomiRs) Related to Countermeasures

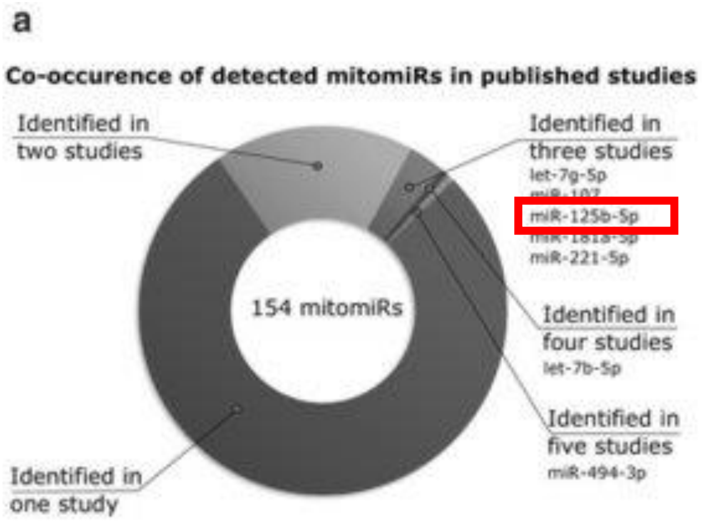
Cell. Mol. Life Sci. (2017) 74:631–646
DOI 10.1007/s00018-016-2342-7
Cellular and Molecular Life Sciences

REVIEW

CrossMark

Interplay of mitochondrial metabolism and microRNAs

Julian Geiger[1] · Louise T. Dalgaard[1]



ELSEVIER
Life Sciences
Volume 164, 1 November 2016, Pages 60-70

miR-15a/miR-16 induces mitochondrial dependent apoptosis in breast cancer cells by suppressing oncogene BMI1

Nibedita Patel [a, 1], Koteswara Rao Garikapati [a, 1], M. Janaki Ramaiah [a, b], Kavi Kishor Polavarapu [d], Utpal Bhadra [c], Manika Pal Bhadra [a]

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https://doi.org/10.1016/j.lfs.2016.08.028

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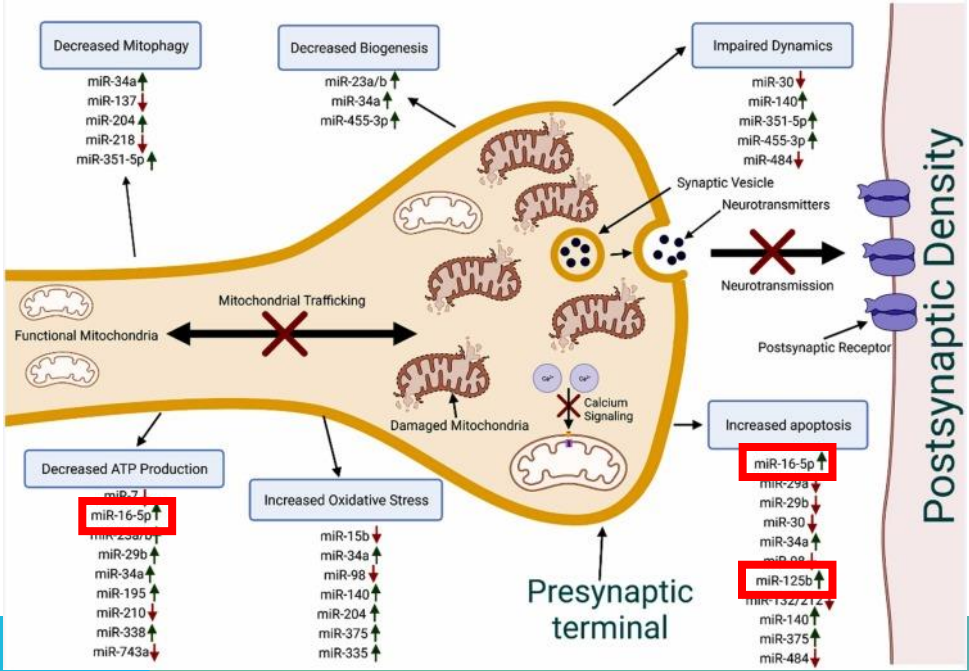

Research Article

Combinatorial Effect of DCA and Let-7a on Triple-Negative MDA-MB-231 Cells: A Metabolic Approach of Treatment

Integrative Cancer Therapies
Volume 19: 1–11
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SAGE

Praveen Sharma, MSc[1] and Sandeep Singh, PhD[1]

Abstract
Dichloroacetate (DCA) is a metabolic modulator that inhibits pyruvate dehydrogenase activity and promotes the influx of pyruvate into the tricarboxylic acid cycle for complete oxidation of glucose. DCA stimulates oxidative phosphorylation (OXPHOS) more than glycolysis by altering the morphology of the mitochondria and supports mitochondrial apoptosis. As a consequence, DCA induces apoptosis in cancer cells and inhibits the proliferation of cancer cells. Recently, the role of miRNAs has been reported in regulating gene expression at the transcriptional level and in reprogramming energy metabolism. In this article, we indicate that DCA treatment leads to the upregulation of let-7a expression, but DCA-induced cancer cell death is independent of let-7a. We observed that the combined effect of DCA and let-7a induces apoptosis, reduces reactive oxygen species generation and autophagy, and stimulates mitochondrial biogenesis. This was later accompanied by stimulation of OXPHOS in combined treatment and was thus involved in metabolic reprogramming of MDA-MB-231 cells.

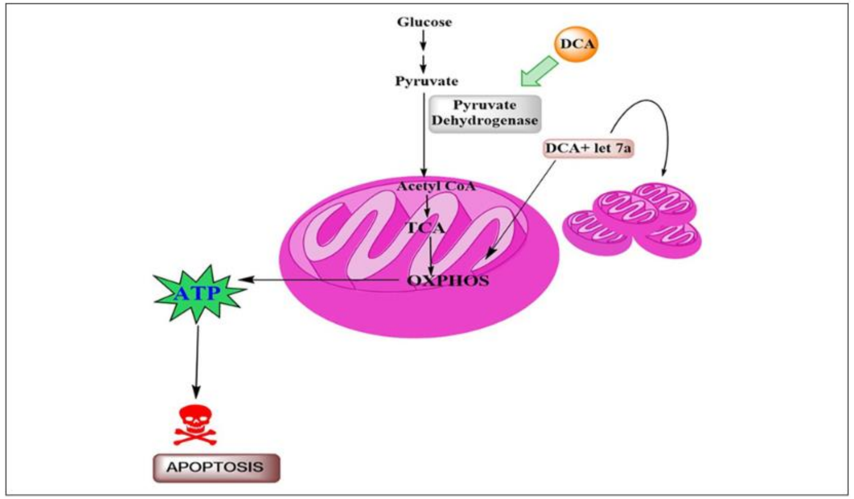

Figure 6. Model showing how combined treatment of let-7a and dichloroacetate (DCA) induces apoptosis by altering mitochondrial morphology and metabolism.

BMC Part of Springer Nature
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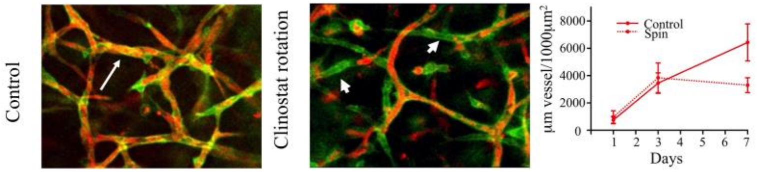
Primary Research | Open Access | Published: 27 November 2021

Let-7a induces metabolic reprogramming in breast cancer cells via targeting mitochondrial encoded ND4

Praveen Sharma, Vibhuti Sharma, Tarunveer Singh Ahluwalia, Nilambra Dogra, Santosh Kumar & Sandeep Singh

Cancer Cell International 21, Article number: 629 (2021)

Targeted Based miRNA Therapy Mitigates Space Radiation Health Risks!!



- Utilized 3D human microvascular tissu models to determine functional impac of miRNAs and start development o miRNA based countermeasures.
- After 0.5Gy GCR irradiation Mature Vessels Collapse
- Applied combination of all 3 self delivery antagomirs (AUM Biotech www.aumbiotech.com) **24 hours prio irradiation** at 0.5µM for each antagomir, then cultured for 6 day after IR.

Simplified GCR Sim Irradiation

Ion species	Energy (MeV/n)	LET (keV /µm)	Dose (mGy)	Dose fraction (mGy)
Proton	1000	0.2	175	0.35
^{28}Si	600	50.4	5	0.01
^{4}He	250	1.6	90	0.18
^{16}O	350	20.9	30	0.06
^{56}Fe	600	173	5	0.01
Proton	250	0.4	195	0.39

Peter Grabham

Columbia University Irving Medical Center

AUM*silence* : 3rd Gen ASO Technology

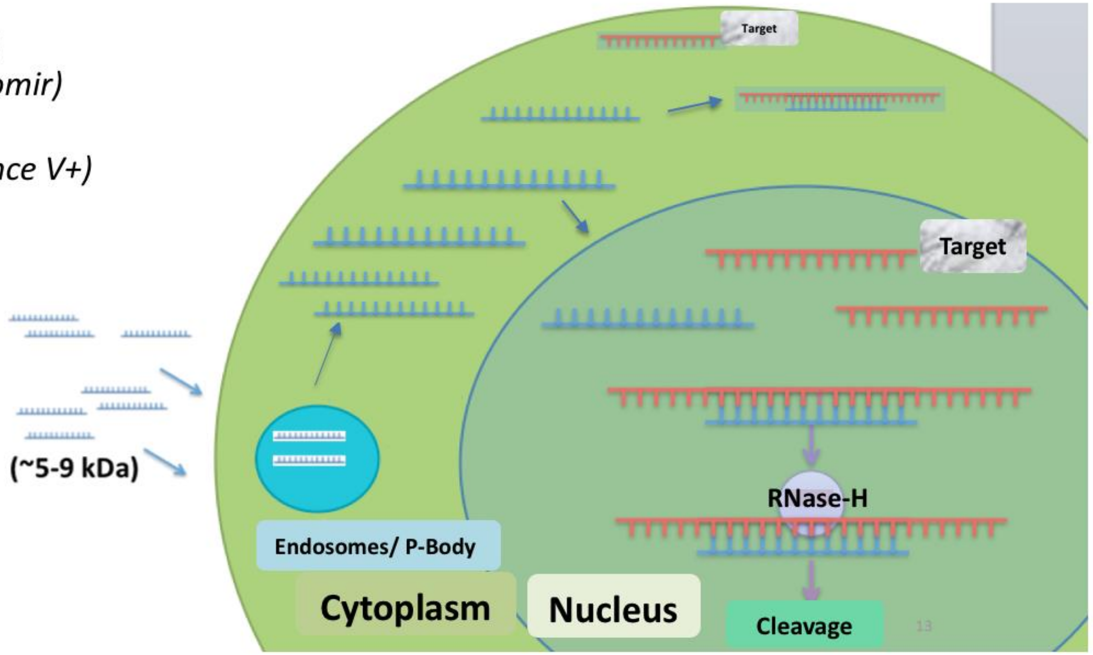
aum BIOTECH

Chemistry is the Key

- ✓ Self-delivery
- ✓ High Potency
- ✓ High Stability
- ✓ High Sequence Specificity
- ✓ Can Target Cytoplasmic & Nuclear RNA

Target:

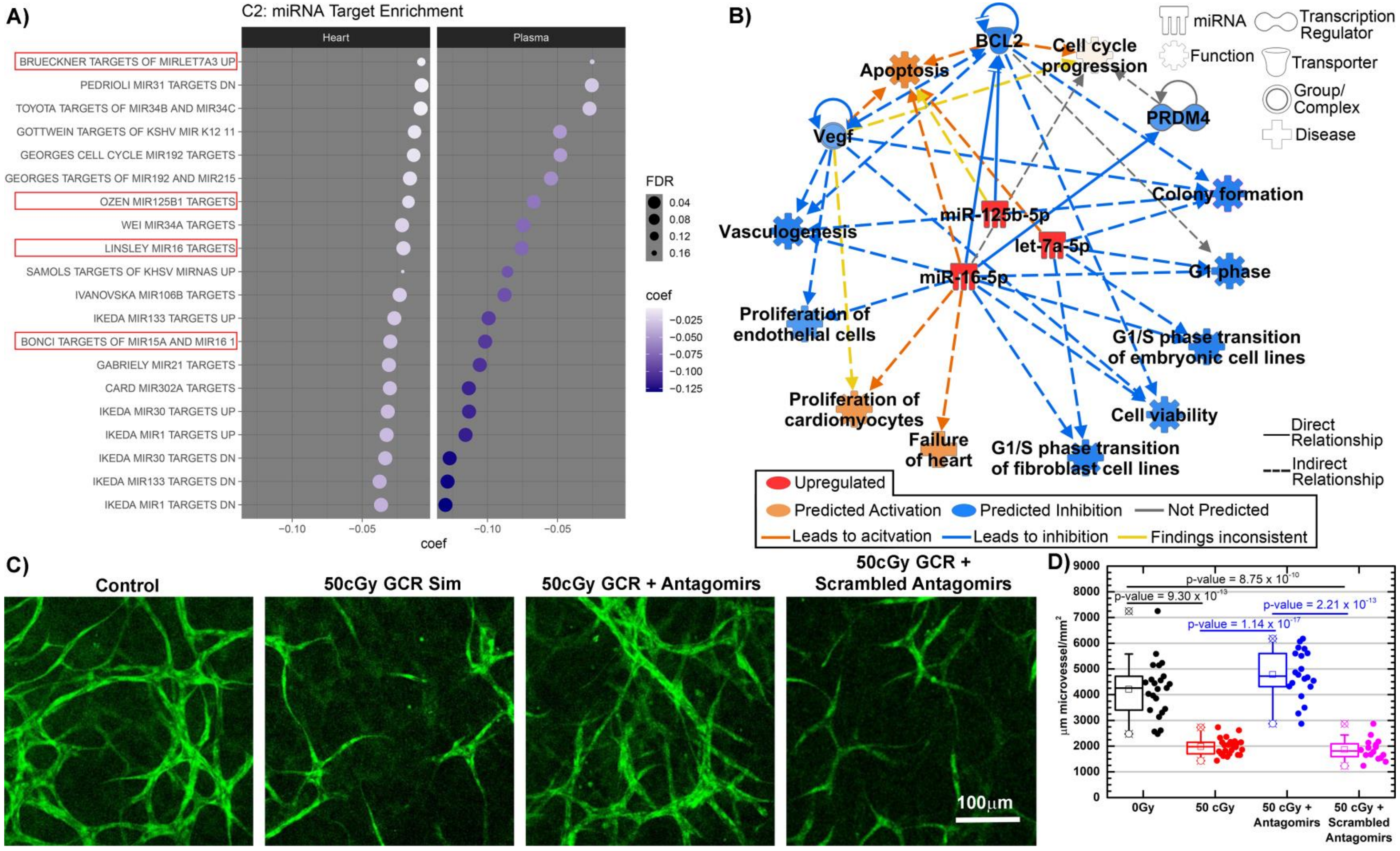
- **mRNA** (AUM*silence*)
- **miRNA** (AUM*antagomir)*
- **lncRNA** (AUM*lnc)*
- **Viral RNA** (AUM*silence V+)*

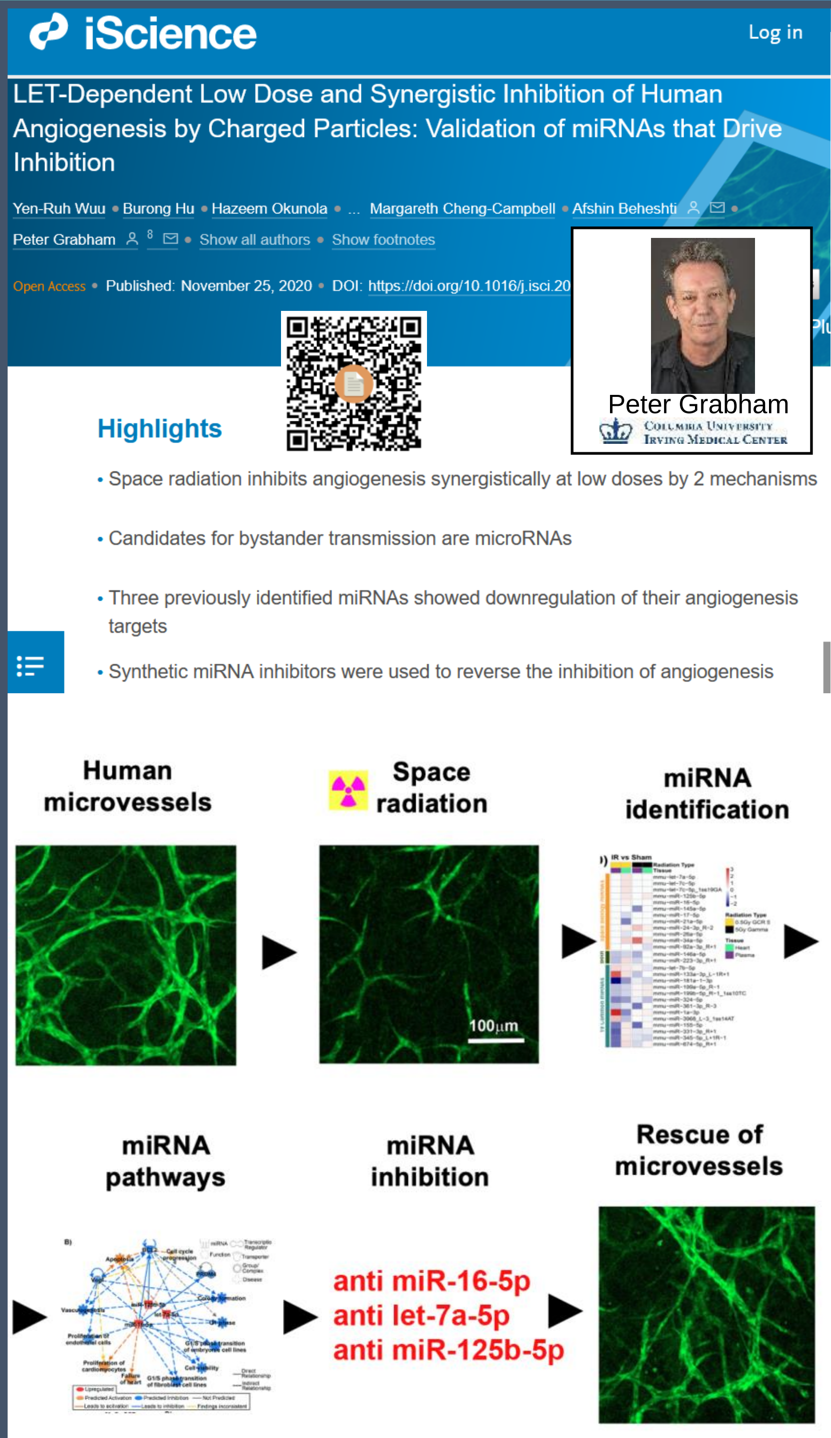


Veenu Aishwarya

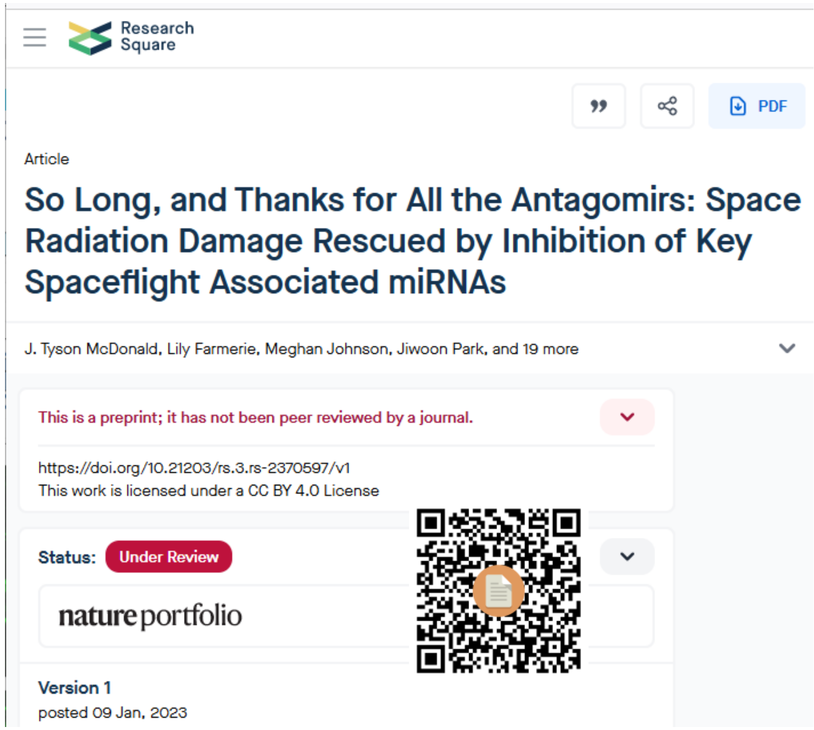
aum LIFETECH

miRNAs impact on Angiogenesis and Antagomir Countermeasures





Combination and Single Antagomir Treatment


Research Square

Article

So Long, and Thanks for All the Antagomirs: Space Radiation Damage Rescued by Inhibition of Key Spaceflight Associated miRNAs

J. Tyson McDonald, Lily Farmerie, Meghan Johnson, Jiwoon Park, and 19 more

This is a preprint; it has not been peer reviewed by a journal.

https://doi.org/10.21203/rs.3.rs-2370597/v1

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Status: Under Review

nature portfolio

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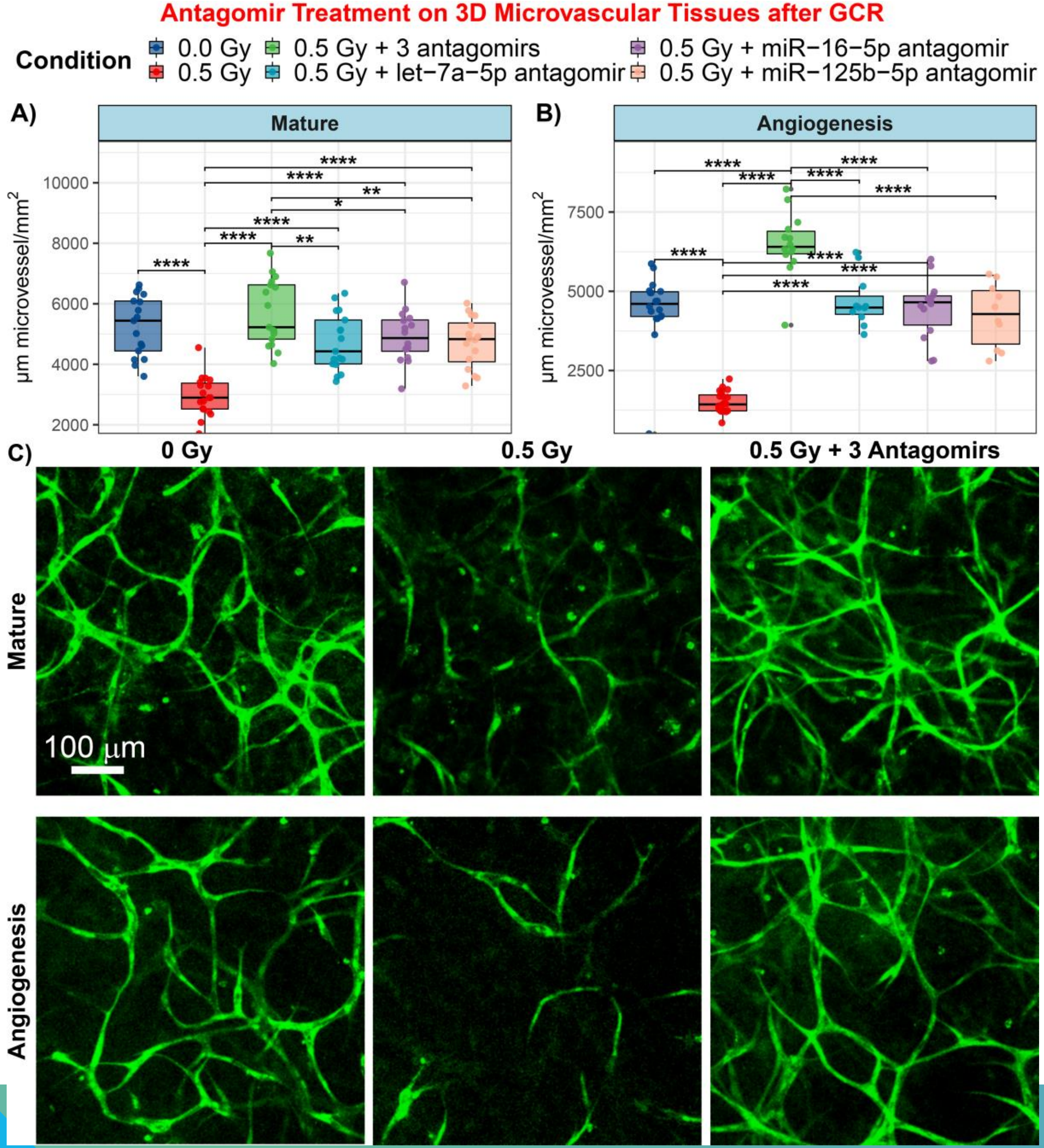

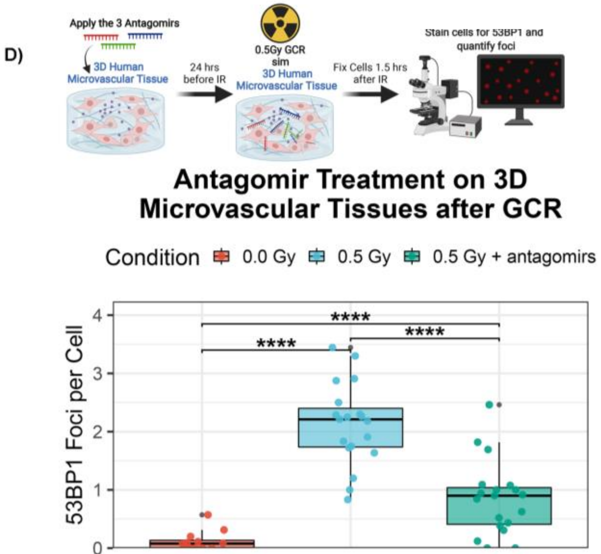

* p-value < 0.05

** p-value < 0.01

*** p-value < 0.001

**** p-value < 0.0001

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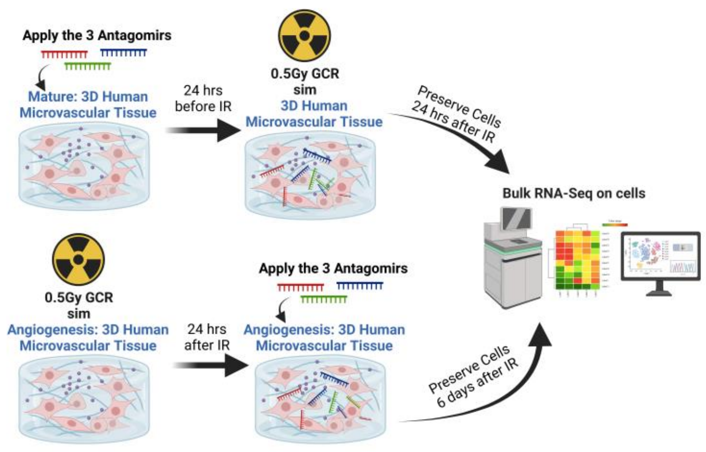
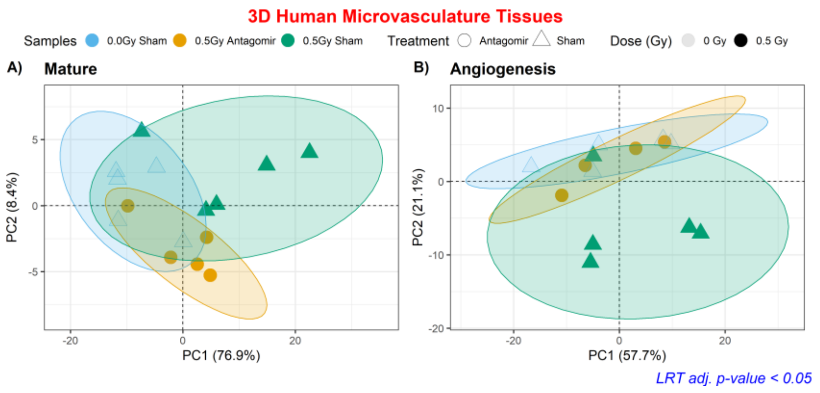
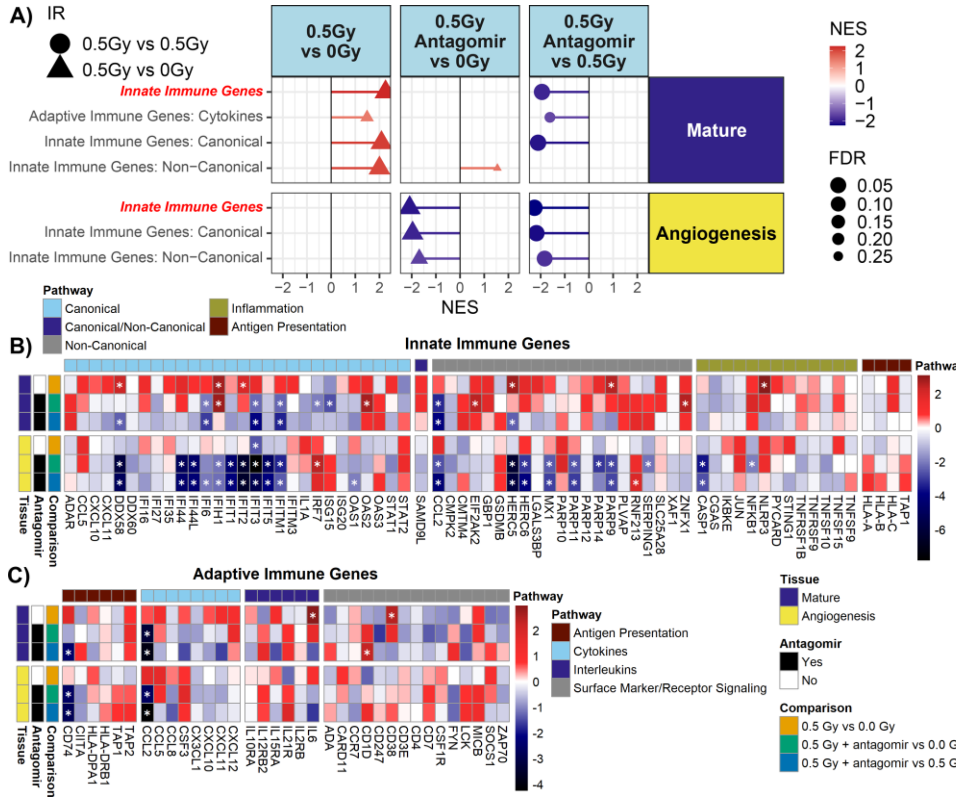
Manuscript under review

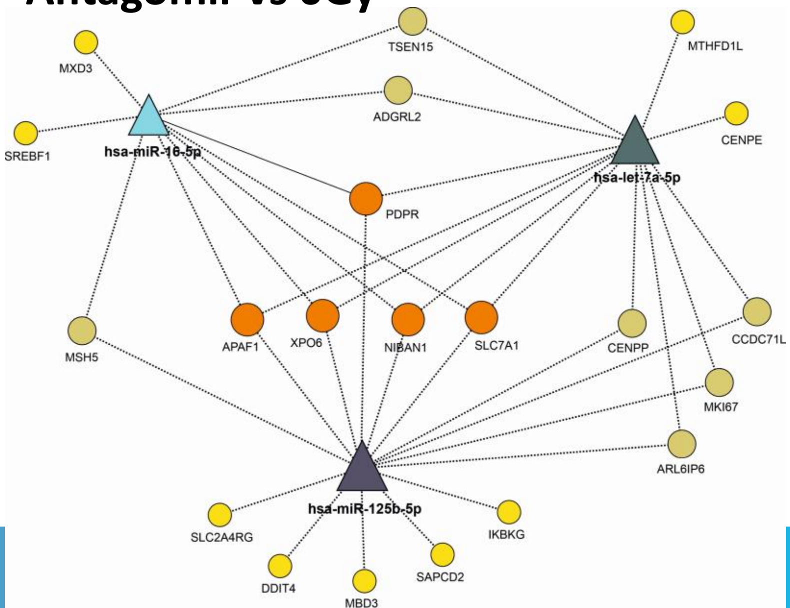
In vitro experiments with antagomirs: Further analysis with the impact of antagomirs on the 3D tissue model





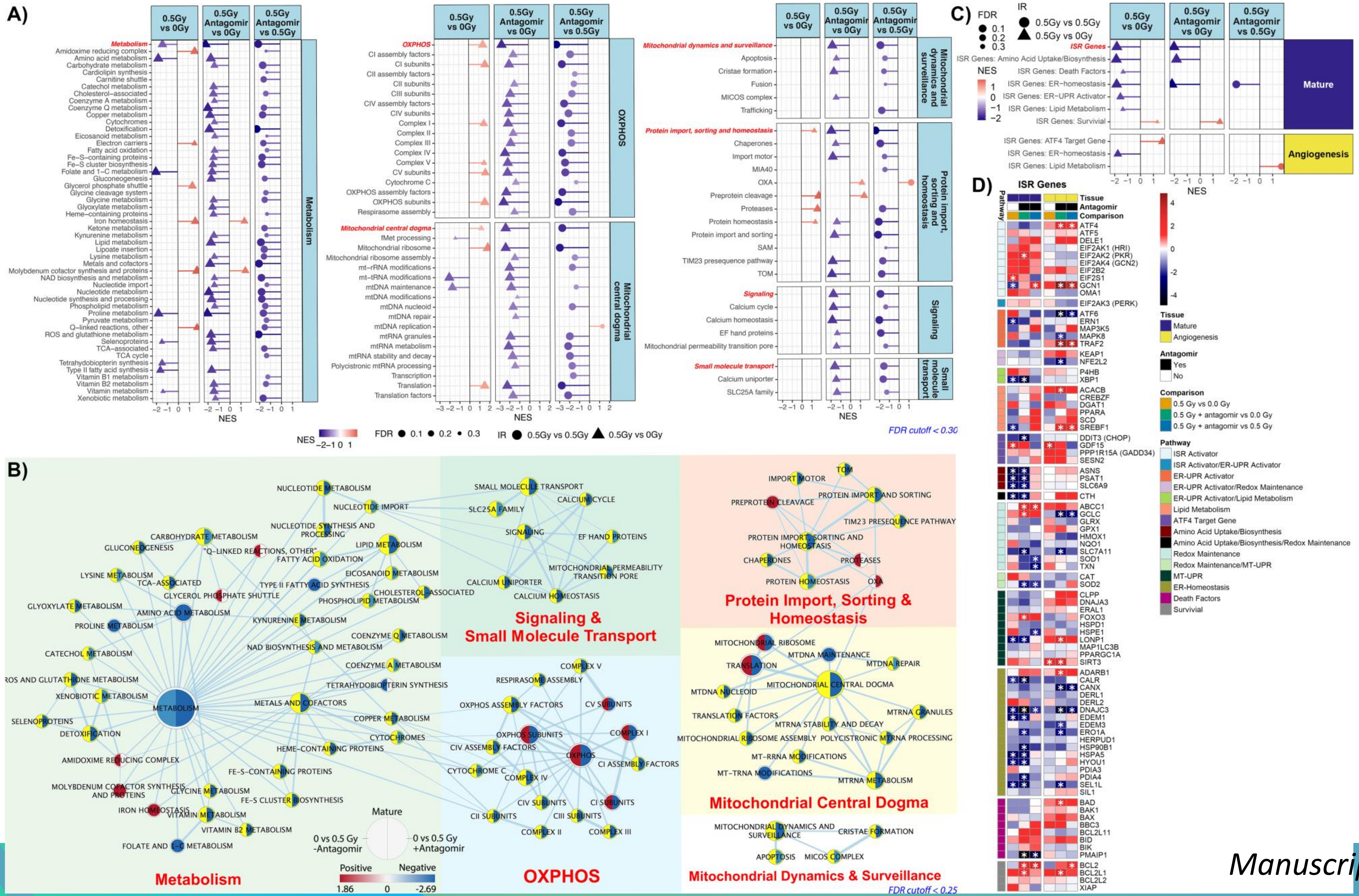


Significantly Regulated Gene targets for all 3 miRNAs with 0.5Gy vs 0Gy, but are not significant anymore for 0.5Gy Antagomir vs 0Gy



Manuscript under review

Further analysis with the impact of antagomirs on the 3D tissue Mature model: Mitochondrial Impact!



Manuscript under review

In vivo experiments with antagomirs: Cardio... Enviro...

Peter Jirak

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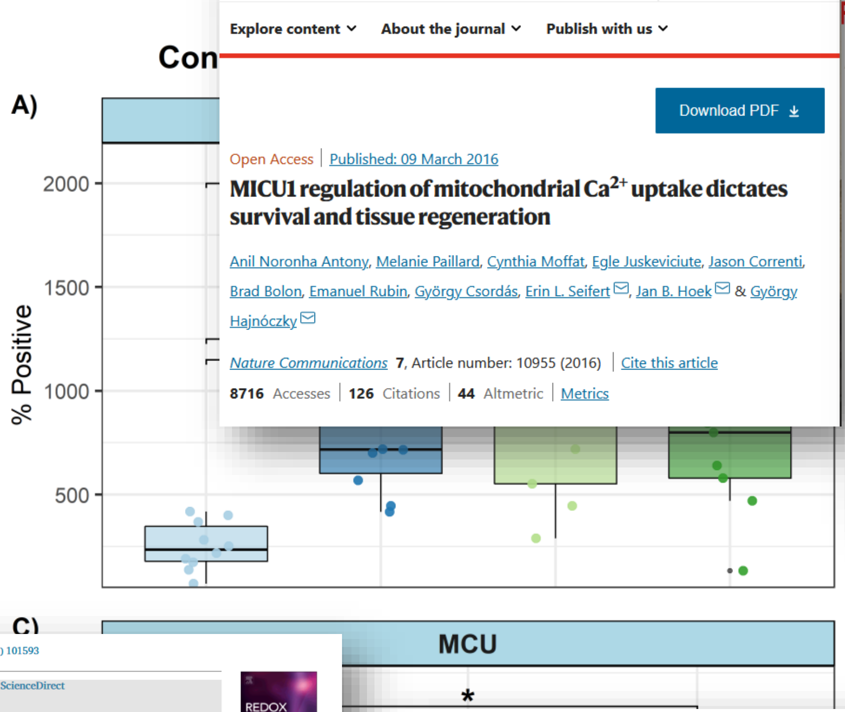

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MICU1 regulation of mitochondrial Ca^{2+} uptake dictates survival and tissue regeneration

Anil Noronha Antony, Melanie Paillard, Cynthia Moffat, Egle Juskeviciute, Jason Correnti, Brad Bolon, Emanuel Rubin, György Csordás, Erin L. Seifert, Jan B. Hoek & György Hajnóczky

Nature Communications 7, Article number: 10955 (2016) | Cite this article

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TGF-β1 attenuates mitochondrial bioenergetics in pulmonary arterial endothelial cells via the disruption of carnitine homeostasis

Xutong Sun[a], Qing Lu[a], Manivannan Yegambaram[a], Sanjiv Kumar[b], Ning Qu[a], Anup Srivastava[a], Ting Wang[c], Jeffrey R. Fineman[c], Stephen M. Black[a,*]

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ABSTRACT

Transforming growth factor beta-1 (TGF-β1) signaling is increased and mitochondrial function is decreased in multiple models of pulmonary hypertension (PH) including lambs with increased pulmonary blood flow (PBF) and pressure (Shunt). However, the potential link between TGF-β1 and the loss of mitochondrial function has not been investigated and was the focus of our investigations. Our data indicate that exposure of pulmonary arterial endothelial cells (PAEC) to TGF-β1 disrupted mitochondrial function as determined by enhanced mitochondrial ROS generation, decreased mitochondrial membrane potential, and disrupted mitochondrial bioenergetics. These events resulted in a decrease in cellular ATP levels, decreased hsp90/eNOS interactions and attenuated shear-mediated NO release. TGF-β1 induced mitochondrial dysfunction was linked to a nitration-mediated activation of Akt1 and the subsequent mitochondrial translocation of endothelial NO synthase (eNOS) resulting in the nitration of carnitine acetyl transferase (CrAT) and the disruption of carnitine homeostasis. The increase in Akt1 nitration correlated with increased NADPH oxidase activity associated with increased levels of $p47^{phox}$, $p67^{phox}$, and Rac1. The increase in NADPH oxidase was associated with a decrease in peroxisome proliferator-activated receptor type gamma (PPARγ) and the PPARγ antagonist, GW9662, was able to mimic the disruptive effect of TGF-β1 on mitochondrial bioenergetics. Together, our studies reveal for the first time, that TGF-β1 can disrupt mitochondrial function through the disruption of cellular carnitine homeostasis and suggest that stimulating carinitine homeostasis may be an avenue to treat pulmonary vascular disease.

REVIEW article

Front. Cardiovasc. Med., 25 January 2021 | https://doi.org/10.3389/fcvm.2020.588347

Pivotal Role of TGF-β/Smad Signaling in Cardiac... Non-coding RNAs as Effectual Players

Somayeh Saadat[1], Mahdi Noureddini[1], Maryam Mahjoubin-Tehran[2], Layla Shojaie[4], Michael Aschner[5], Behnaz Maleki[1], Mohammad Abb... Hasan Rajabi Moghadam[7*], Behrang Alani[8*] and Hamed Mirzaei[9*]

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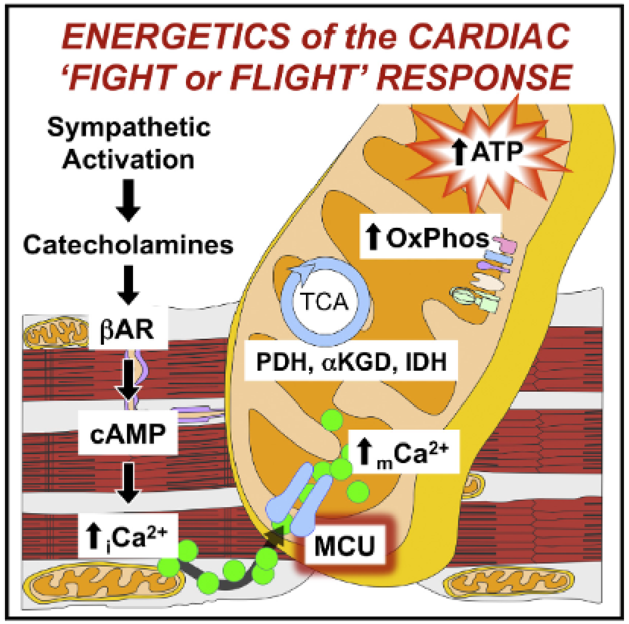
Cell Reports

The Mitochondrial Calcium Uniporter Matches Energetic Supply with Cardiac Workload during Stress and Modulates Permeability Transition

Graphical Abstract



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In Brief

Luongo et al. show, using a conditional knockout mouse model, that the mitochondrial Ca^{2+} uniporter (MCU), although dispensable for homeostatic function, is necessary for the cardiac "fight-or-flight" contractile response and a significant contributor to mitochondrial permeability transition during ischemia-reperfusion injury.

Highlights

- The MCU is dispensable for baseline homeostatic cardiac function
- Deletion of *Mcu* protects against myocardial IR injury by reducing MPTP activation
- The MCU is required to match energetics with contractile demand during stress
- A slow MCU-independent uptake mechanism may maintain basal matrix $_mCa^{2+}$ content

Luongo et al., 2015, Cell Reports 12, 23–34
July 7, 2015 ©2015 The Authors
http://dx.doi.org/10.1016/j.celrep.2015.06.017

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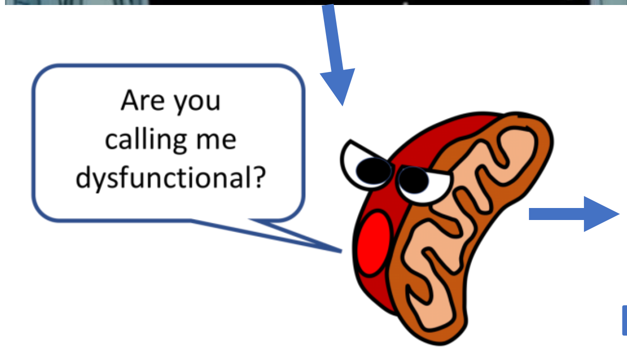
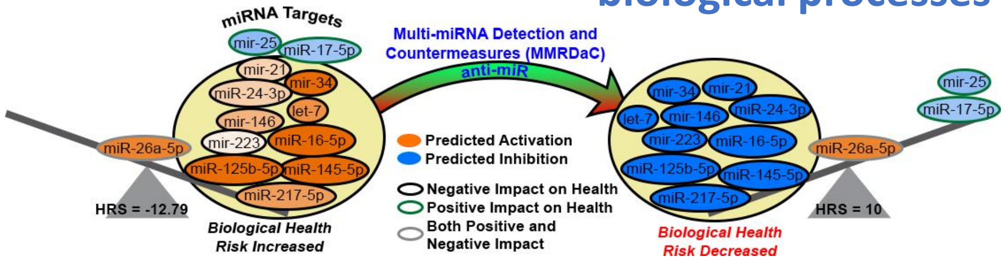
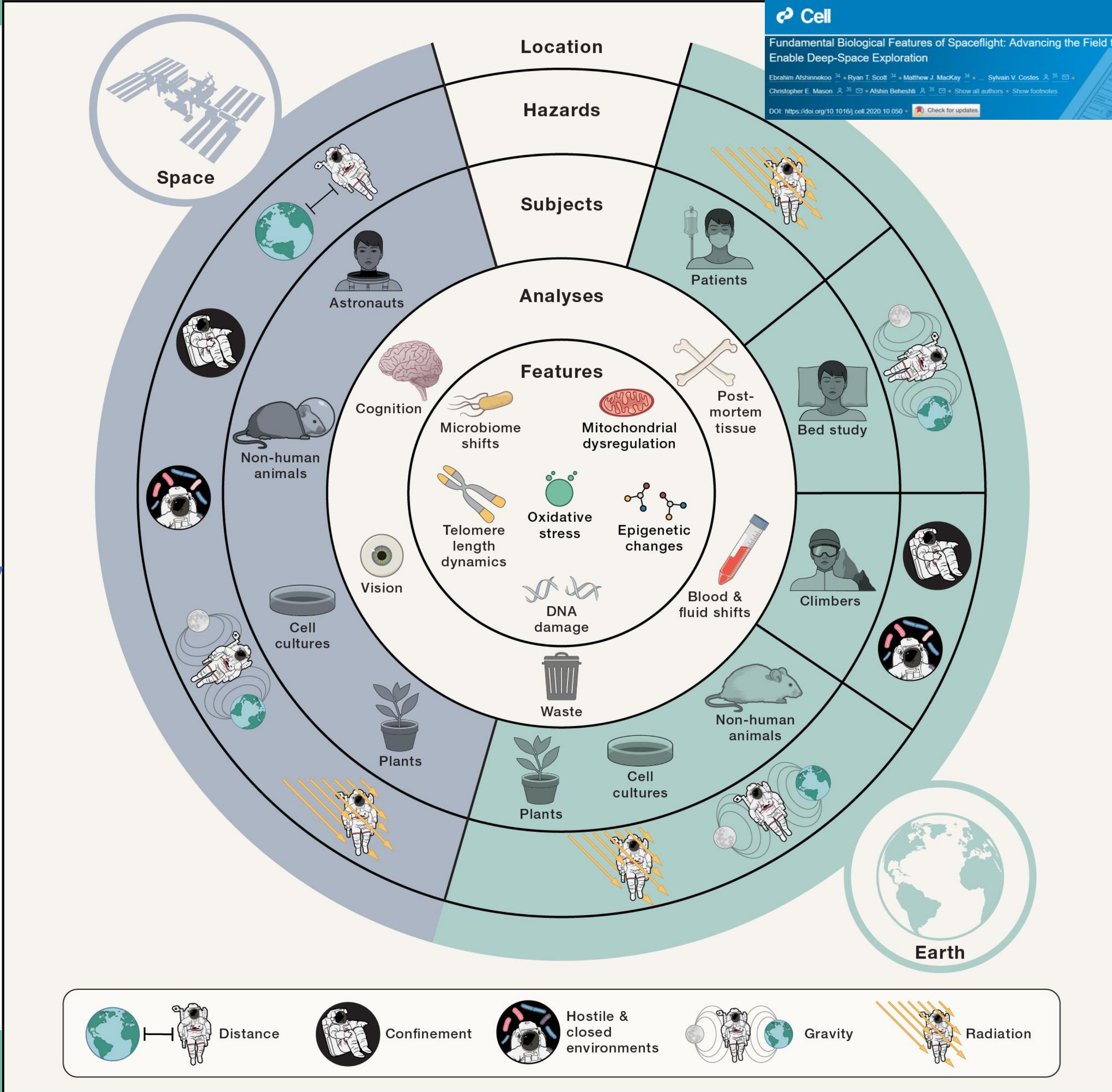
Summary of the Work



Dysregulates other key biological processes



- This spaceflight associated miRNA signature can be a novel minimally invasive biomarker to monitor increased health risks for long-term space missions.
- Also can be used for development of novel miRNA based therapeutic/countermeasure



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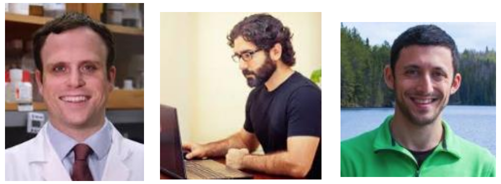
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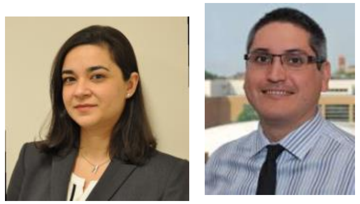
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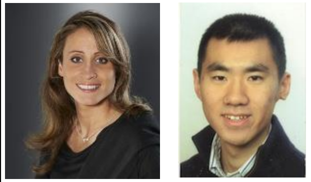
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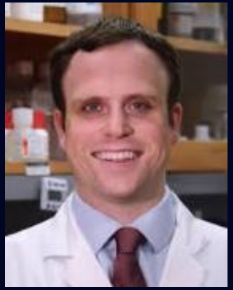

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